Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks

Final Evidence Report

December 20, 2018

Prepared for

Authors:

ICER Staff/Consultants*	University of Colorado Skaggs School of Pharmacy Modeling Group†
Jeffrey A. Tice, MD Professor of Medicine University of California, San Francisco **Judith M. E. Walsh, MD, MPH** Professor of Medicine University of California, San Francisco **Patricia Synnott, MALD, MS** Senior Research Lead, Evidence Synthesis Institute for Clinical and Economic Review **Varun M. Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Ellie Adair, MPA** Program Manager Institute for Clinical and Economic Review **David Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review **None of the above authors have any conflicts of interest to disclose*	**Jonathan D. Campbell, PhD** Associate Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research **Melanie D. Whittington, PhD** Research Instructor Department of Clinical Pharmacy **R. Brett McQueen, PhD** Assistant Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research **Samuel McGuffin, MPH** Professional Research Assistant Department of Clinical Pharmacy **Sean Sullivan, PhD** Professor and Dean University of Washington School of Pharmacy †*The role of the University of Colorado Skaggs School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UC. None of the above modelers have any conflicts of interest to disclose*

DATE OF PUBLICATION: December 20, 2018

Jeff Tice served as the lead author for this report, with assistance from Judith Walsh. Jeff Tice, Judith Walsh, and Patricia Synnott led the systematic review and authorship of the comparative clinical effectiveness section. Varun Kumar was responsible for oversight of the cost-effectiveness analyses and developing the budget impact model. The role of the University of Colorado Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the University of Colorado. Madeline O'Grady authored the section on coverage policies and clinical guidelines, with oversight from Ellie Adair. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Aqsa Mugal, Ariel Jurmain, Milon Waththuhewa, Laura Cianciolo, and Madeline O'Grady 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. 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.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 20% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: AstraZeneca, Genentech, GlaxoSmithKline, Regeneron, and Sanofi. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – 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. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council 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 Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/asthma-stakeholder-list-2018/

Expert Reviewers

Kenneth Mendez
President and Chief Executive Officer
The Asthma and Allergy Foundation of America
Mr. Mendez personally owns stock in health care companies, but in an amount of less than $10,000. The AAFA receives greater than 25% of their funding to produce educational materials and for patient research through grants from pharmaceutical companies, including AstraZeneca, Genentech, GSK, Sanofi/Regeneron, and Teva.

Matt Stevenson, PhD
Professor of Health Technology Assessment
University of Sheffield
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

David Stukus, MD
Associate Professor of Pediatrics
Nationwide Children's Hospital
The Ohio State University College of Medicine
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

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
LTRA	Leukotriene receptor antagonist
MAC	Medicare Administrative Contractor
MART	Maintenance and reliever therapy
NCD	National coverage determination
NHE	National health expenditures
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
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

The Centers for Disease Control and Prevention (CDC) estimates that 20.4 million Americans ages ≥18 years currently have asthma and an additional 6.1 million children have asthma.[1,2] There are approximately 14.2 million office visits, 1.8 million emergency room visits, and 440,000 hospitalizations due to asthma each year in the US.[2] The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma related mortality, and $3 billion from missed work and school.[2] Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[3]

Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells.[4] These cells secrete IL-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[5,6] The medications evaluated in this review target specific components of these pathways and may be more effective in specific asthma patient subgroups.

There are five FDA approved monoclonal antibodies that affect the pathways involved in either the allergic or type 2 inflammatory phenotypes of asthma. The drugs, dosing, their mechanisms of action, and their FDA indications for asthma are summarized in Table ES1 below. Omalizumab is a monoclonal antibody to IgE, which is indicated for the treatment of patients with moderate to severe asthma with the allergic phenotype described above. Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway either with monoclonal antibodies to IL-5 itself (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab). Dupilumab is a monoclonal antibody to the IL-4 receptor alpha, which modulates both the IL-4 and IL-13 pathways.

Table ES1. Monoclonal Antibody Therapies for Type 2 Inflammation in Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®, Genentech)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens[7]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[8]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[9]
Benralizumab (Fasenra™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[10]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma[11]

There are important differences in the indications for each of the drugs including age, severity of asthma, and asthma phenotype. These differences are reflected in the study populations enrolled in the pivotal trials for each drug and make comparisons between drugs challenging. In addition, dupilumab is the only drug approved for self-administration; the other four drugs must be administered by a health care professional.

Insights Gained from Discussions with Patients and Patient Groups

The most important insight gained from speaking with patients was their heartfelt desire to be able to perform their day to day tasks of living – to get back to their usual activities of daily living. Symptom relief, asthma control, and quality of life matter much more to them than a reduction in asthma exacerbations. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

The Asthma and Allergy Foundation of America shared results from their survey of 805 Americans living with asthma including 185 with severe, uncontrolled asthma.[12] The two most important factors for choosing a therapy for both groups were effectiveness and then cost. However, effectiveness was the far more important factor for patients surveyed. An average of 82%

responded that effectiveness was a key criterion while an average of 52% cited cost as a key criterion.

Potential Cost-Saving Measures in Asthma

Stakeholders did not identify any potential cost-saving measures.

The Choosing Wisely statement from the **American Academy of Allergy, Asthma & Immunology** includes the following:

Don't diagnose or manage asthma without spirometry.

"Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore, spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment."[13]

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of the five biologics added to standard of care (SoC) versus SoC alone, we abstracted evidence from RCTs of individuals ages six years and older with moderate to severe allergic asthma or eosinophilic asthma. The comparator treatment for each intervention of interest included SoC treatment with ICS and at least one additional controller agent. Our review focused on clinical benefits (i.e., asthma exacerbations, ED visits, hospitalizations, quality of life (AQLQ, ACQ, SGRQ) as well as potential harms (severe adverse events, adverse events leading to discontinuation of therapy).

Clinical Benefits

Reduction in Exacerbation Rates Requiring Systemic Steroids

There were no head to head randomized or observational trials of the five monoclonal antibodies. The summary estimates from Cochrane meta-analyses[14,15] for each of the drugs are summarized in Table ES2 below in addition to the estimates for dupilumab from the pivotal trials.[16-18] As can be seen in the table, all five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics. For instance, the relative rates have been shown to be consistently lower (greater efficacy) for each of the drugs

in populations with higher baseline eosinophil counts.[16-20] If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table ES2.

Table ES2. Rate Ratio for Asthma Exacerbations Requiring Steroid Therapy

Treatment	Rate Ratio (95% CI)
Omalizumab	0.52 (0.37-0.73)
Mepolizumab	0.45 (0.36-0.55)
Reslizumab	0.43 (0.33-0.55)
Benralizumab	0.59 (0.51-0.68)
Dupilumab 200 mg	0.44 (0.34-0.58)
Dupilumab 300 mg	0.40 (0.31-0.53)

Measures of Health-Related Quality of Life and Asthma Control

The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is more important to patients and to the long-term value of the therapy.

The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points. The average AQLQ score prior to therapy in the studies was close to four across all of the studies.

Table ES3. Mean Difference in AQLQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	0.26 (0.05-0.47)
Mepolizumab	NR
Reslizumab	0.28 (0.17-0.39)
Benralizumab	0.23 (0.11-0.35)
Dupilumab 200 mg	0.29 (0.15-0.44)
Dupilumab 300 mg	0.26 (0.12-0.40)

AQLQ: Asthma Quality of Life Questionnaire, NR: not reported

As can be seen in Table ES3 above, the average improvement for four of the drugs compared with placebo is modest and none of them reach the minimally important difference, although all were statistically significant. The trials of mepolizumab using the FDA approved SC formulation did not report AQLQ outcomes data. As with the estimates for asthma exacerbations, the change in AQLQ estimates for each drug in Table ES3 come from different populations, so comparisons between drugs are uncertain due to potential selection bias.

The ACQ is a seven-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points. The average ACQ score prior to therapy in the studies was close to 2.5 across most of the studies (see Appendix Table D1).

Table ES4. Mean Difference in ACQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	NR
Mepolizumab	-0.42 (-0.56 to -0.28)
Reslizumab	-0.27 (-0.36 to -0.19)
Benralizumab	-0.23 (-0.34 to -0.12)
Dupilumab 200 mg	-0.39 (-0.53 to -0.25)
Dupilumab 300 mg	-0.22 (-0.36 to -0.08)

ACQ: Asthma Control Questionnaire

As with the AQLQ, the improvements in the ACQ compared with placebo were clinically modest, but statistically significant for the four drugs that reported this outcome in randomized trials (Table ES4).

Some of the trials of mepolizumab also reported changes in the SGRQ. The SGRQ is a 50-item questionnaire focusing on overall health, daily life, and perceived well-being. It is scored from zero to 100 with higher numbers representing greater limitations. The minimally important difference is four points. The SGRQ has been used in COPD but has been extensively validated in patients with asthma.[21-25] The summary estimate for mepolizumab compared with placebo was -7.40 points (95% CI: -9.50 to -5.29). By this measure, the average patient treated with mepolizumab had a clinically meaningful improvement in quality of life, even though this was not observed with the ACQ in these trials.

Patients with Blood Eosinophils ≥ 300 cells/µL, ≥ 2 Exacerbations in the Prior Year, and ACQ ≥ 1.5

Four of the five biologic drugs considered in this review are indicated for eosinophilic asthma and the fifth drug has published data suggesting that there are greater relative reductions in exacerbation rates for patients with eosinophils ≥ 300 cells/µL compared with patients with lower eosinophil counts (see Table ES5 below).[16,19] We performed a network meta-analysis in the subgroup of patients with eosinophils ≥ 300 cells/µL, two or more exacerbations in the year prior to randomization, and an ACQ ≥ 1.5 because the benefits seemed greater in this population and because it may represent a more homogenous population.

Table ES5. Rate Ratio for Asthma Exacerbations by Eosinophil Level

Treatment	Eos < 300 (95% CI)	Eos ≥ 300 (95% CI)
Omalizumab	1.07 (0.45-2.53)	0.41 (0.20 -0.80)

Eos: blood eosinophils (cells/µL)

Table ES6 below shows the pairwise comparisons for all of the drugs as well as placebo.

Table ES6. NMA Results Comparing the Relative Rate of Asthma Exacerbations for Five Biologic Therapies

Dupilumab200						
1.00 (0.33, 3.00)	Dupilumab300					
0.78 (0.15, 4.09)	0.78 (0.15, 4.20)	Omalizumab				
0.75 (0.16, 3.70)	0.75 (0.16, 3.69)	0.97 (0.18, 5.20)	Reslizumab			
0.72 (0.18, 2.89)	0.72 (0.18, 2.87)	0.92 (0.21, 4.10)	0.95 (0.24, 3.86)	Mepolizumab		
0.44 (0.11, 1.74)	0.44 (0.11, 1.76)	0.57 (0.13, 2.41)	0.59 (0.15, 2.30)	0.62 (0.20, 1.89)	Benralizumab	
0.26 (0.08, 0.79)	**0.26 (0.08, 0.80)**	0.33 (0.10, 1.14)	0.34 (0.11, 1.03)	**0.36 (0.16, 0.81)**	0.59 (0.26, 1.29)	Placebo

Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

In Table ES6, only dupilumab (both doses) and mepolizumab were significantly better than placebo likely due to relatively small numbers of patients in this subgroup for omalizumab, mepolizumab and benralizumab. The point estimates for omalizumab, reslizumab, and mepolizumab were nearly identical. Dupilumab had the largest reduction in exacerbations and benralizumab the smallest, but none of the comparisons between drugs were statistically significant. The estimates for the RR for dupilumab, omalizumab, reslizumab, and mepolizumab are markedly better than those reported in the full trial, but the NMA estimate for benralizumab is nearly identical to its primary estimate, because it was studied in patients with severe asthma, an ACQ ≥ 1.5, at least two exacerbations in the prior year, and a baseline eosinophil count ≥ 300 cells/µL.

Harms

All five drugs were well tolerated. The risk for serious adverse events was lower in the active drug group than the placebo group for all five drugs. There were no differences in withdrawals due to adverse events except for an increase in drug discontinuation rates for the 300 mg dose of dupilumab. However, there was a significant reduction in discontinuation due to adverse events for dupilumab at the 200 mg dose, so this may be a chance finding. The only consistent adverse event that was more common in the drug arm of the randomized trials compared with the placebo arm was injection site reactions. They were about twice as common in the drug arm as in the placebo arm for most the drugs. Reslizumab was the exception, which may be due to the IV administration of the drug.

Controversies and Uncertainties

There are several important uncertainties. First, there is a lack of evidence on the long-term safety and effectiveness of these drugs, particularly in older patients, given that many of the patients taking the drugs are relatively young when they start and have 30 to 70-year life expectancies. The length of follow-up in some of the randomized trials was only 24 weeks and no trial was longer than 15 months. The long-term extension trials and real-world experience with omalizumab and mepolizumab are reassuring, but uncontrolled.

There is no clear definition for a response to therapy to help guide patients and clinicians in deciding when to stop one therapy for insufficient effect and consider switching to another. Similarly, apart from the allergic phenotype and eosinophilia, there are currently no biomarkers to help clinicians decide which of these drugs may be most appropriate for the individual patient confronting the decision to start one of these drugs.

While quality of life is an essential driver of the overall evaluation of the effectiveness of these therapies, there is no standard assessment of quality of life used across all studies. Ideally, there would be one measure, assessed at a standard time point, that could be used to compare quality of life across interventions.

Eosinophils are part of the immune response to parasitic infections. It is unknown if the therapies that decrease eosinophil counts will affect patients' ability to fight such infections. Current guidelines recommend that physicians treat patients for existing parasitic infections prior to initiating anti IL-5 therapy.

Finally, the current evidence base precludes reliable comparative effectiveness analyses between the five drugs as highlighted by Drs. Drazen and Harrington in their editorial accompanying the publication of the pivotal trials of dupilumab.[26] They assert that they regard the treatments targeting type 2 inflammation "as essentially equivalently effective treatments." They call for researchers to design and implement a large, pragmatic trial comparing all of the available drugs in order to clarify whether or not there are clinically important differences between the drugs and to facilitate studies of biomarkers that could identify subgroups of patients likely to benefit from one of the specific drugs.[26]

Summary and Comment

Results from our review of the drugs currently approved for uncontrolled moderate to severe asthma suggest that they are safe and effective. All five drugs reviewed reduced the number of asthma exacerbations compared with placebo, modestly improved day-to-day quality of life, and available data suggest few harms. None of the drugs prevented most exacerbations requiring systemic corticosteroids or improved average daily quality of life to a degree considered clinically

significant. Thus, the net health benefit for all five drugs is at best incremental. Omalizumab and mepolizumab have the longest follow-up in extension studies of the pivotal trials and the longest real-world data, so the uncertainty about long-term effectiveness and safety is lowest for these two drugs. Dupilumab is the only drug approved for self-administration, which is an important benefit for patients. Reslizumab must be administered IV, which may be important for some patients, but three of the other drugs also require administration by a health care professional, so it is not clear if this is important for patients as all require office visits. Given the requirement for office visits for administration, the every 8 week dosing of benralizumab may be important to some patients.

Because they have greater long-term follow-up and real-world data, we judged the net health benefit of both omalizumab and mepolizumab to be incremental compared with standard of care (B). There is greater uncertainty about the net health benefit of reslizumab, benralizumab, and dupilumab, so we judged their net health benefit to be comparable or better compared with standard of care (C+).

Long-Term Cost Effectiveness

We developed a cost-effectiveness model comparing five biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab), each to standard of care (SoC), for the treatment of moderate to severe uncontrolled asthma with evidence of type 2 inflammation in adults and in children six years and older. This analysis represents an update of our prior analysis on this topic.[27] The population for this updated review was designated with a broad intention to capture the existing or expected FDA indications for all the relevant biologics, though not all of the therapies are indicated for use in younger children or patients with moderate asthma (refer to Table 3.1 in the clinical section). Quality-adjusted survival and health care costs were estimated for each biologic and its relevant comparators using the health care sector perspective. Costs and outcomes were discounted at 3% per year, and were modeled over a lifetime time-horizon, with a model cycle length of two weeks. Incremental costs and outcomes were calculated comparing each intervention to its comparator.

The Markov model included three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst without emergency department (ED) or inpatient care, asthma-related ED visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality).

Key clinical inputs for the model, informed by the evidence review, included exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, asthma control, asthma quality of life, biologic treatment response, and adverse events. Model outcomes for each intervention included total drug and non-drug health care costs,

life years (LY) gained, quality-adjusted life years (QALYs) gained, and annualized asthma exacerbations.

Key Model Characteristics and Assumptions

Presented below are the key model assumptions. The entire list of assumptions and accompanying rationale for each assumption is available in section 4 of the report.

- Base-case utility for the non-exacerbation health state was different for biologic plus SoC versus SoC alone due to potential improvements in day-to-day symptoms.
- Long-term biologic treatment only for treatment responders was included as a scenario analysis for all biologics.
- In order to eliminate differences across baseline characteristics, such as age, that may impact lifetime costs and outcomes, we averaged over baseline characteristics to estimate the same model cohort's baseline age, gender, weight, proportion of chronic oral steroid users, and SoC annualized exacerbation rates.

Model Inputs

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The evidence suggested no differences in costs or disutility values associated with adverse events between biologics plus SoC versus SoC alone. Chronic oral steroid use and its associated long-run costs and disutility was included within this updated review. Asthma-related mortality and other cause mortality were modeled for all living health states (non-exacerbation and exacerbation).[28-31] Health state utilities were derived from publicly available literature and applied to the disease states. The non-exacerbation health state utility value was allowed to be different for the biologic plus SoC treatment arm versus SoC alone. Without known direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we relied on evidence of patient reported outcome instruments with known utility mappings. Disutilities associated with exacerbation events and chronic OCS use were included in the model with duration of disutility being two weeks for the exacerbation events.

Economic Inputs

The unit cost for each intervention is reported in Table ES7. Net price data that were submitted by the five manufacturers were used wherever calculations or reporting involves net price. Treatment-related costs (SoC and asthma biologics) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states). Treatment-related administration and office-visits costs were included. We also included costs of lost productivity associated with treatment with asthma biologics and SoC for the modified societal perspective scenario. Threshold prices

were calculated at the three cost-effectiveness thresholds ($50,000, $100,000 and $150,000 per QALY gained).

Table ES7. Treatment Costs and Details

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Unit	150 mg vial	100 mg	100 mg/ml vial	30 mg	2 x 200mg or 2 x 300mg
Wholesale Acquisition Cost (WAC)	$1,084.66	$2,868.67	$878.80	$4,752.11	$2,931.54
Manufacturer Net Price (% of WAC)	$802.64* (74% of WAC)	$2,272† (79% of WAC)	$804.10‡ (91% of WAC)	$4,265¥ (90% of WAC)	$2,384.62^ (81% of WAC)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns." Benralizumab will have an additional cost of $6,302.30 for the first year of treatment due to the higher frequency of administration for the first three doses.
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone." Dupilumab will have an additional cost of $1,192.31 for the first year of treatment due to the loading dose.

In addition to the base-case analyses, we conducted one-way and probabilistic analyses, as well as specific scenario analyses. Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. Four scenario analyses included within the Executive Summary are as follows: 1. Modified societal perspective; 2. Subpopulation of patients with baseline eosinophil counts ≥300 cells/µL and at least two exacerbations in the previous year; 3. Treatment responder scenario using evidence primarily from omalizumab studies and; 4. Collective best-case analyses using inputs that favor the lifetime value toward that of biologic therapy. A full list of scenario analyses is available in section 4 of the report.

Results

Base-case discounted incremental results are found in Table ES8 with all biologics falling in the $300,000 to $400,000 per QALY range.

Table ES8. Base-Case Incremental Cost-Effectiveness Ratio and Annual Price (side-by-side)

	Base-Case Incremental Cost-Effectiveness Ratio	Annual Price*
Omalizumab	$325,000	$28,900
Mepolizumab	$344,000	$29,500
Reslizumab	$391,000	$28,900
Benralizumab	$371,000	$27,800
Dupilumab	$351,000	$31,000

*Annual price excluding loading dose in year 1 of treatment and excluding administration costs.

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty for mepolizumab versus SoC included utility estimates for the biologic and SoC non-exacerbation health state, annual exacerbation rates for SoC, and cost of chronic oral steroid use (Figure 4.2). Other biologics had similar findings in terms of importance of inputs and relative impact on findings (See Appendix Figures E1- E4).

In probabilistic sensitivity analyses, no biologic achieved a greater than zero likelihood of meeting the $150,000/QALY or lower threshold (Table ES9).

Table ES9. Probabilistic Sensitivity Analysis Results: Biologic versus Standard of Care

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Omalizumab	0%	0%	0%
Mepolizumab	0%	0%	0%
Reslizumab	0%	0%	0%
Benralizumab	0%	0%	0%
Dupilumab	0%	0%	0%

QALY: quality-adjusted life year

Only selected scenario analyses are presented herein. A modified societal perspective, differences in asthma study population characteristics and other features such as responder treatment strategies, and the subpopulation of chronic oral steroid users suggested a bounding of the value assessments toward generally favoring the biologic treatments.

The findings for the collective best-case scenarios that use SoC and relative signals that most favor the biologics suggest incremental cost-effectiveness ratios in the $200,000s and upper $100,000s per QALY. Scenario #1 suggests that when using the most severe of baseline characteristics and largest relative clinical signals and lowest biologic cost, the resulting incremental cost-effectiveness ratio decreases from the $300,000s per QALY to $226,000 per QALY. Further, when restricting the

treated population to only those who are on chronic oral corticosteroids, the resulting incremental cost-effectiveness ratio further decreases to approximately $174,000 per QALY. And when adding the responder scenario alongside assuming favorable clinical and cost inputs, the incremental lifetime findings are approximately $156,000 per QALY. We added the collective best-case scenarios due to public feedback from the draft evidence report. The feedback rightly pointed out differences in the asthma study populations across the assessed biologics.

Threshold Analyses

Table ES10 presents the annual price results for the five biologic agents in the review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) at $50,000, $100,000, and $150,000 per QALY cost-effectiveness thresholds for within-trial and long-run variations.

Table ES10. Threshold Annual Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Omalizumab	$4,700	$9,000	$13,300
Mepolizumab	$5,100	$9,200	$13,400
Reslizumab	$2,900	$6,500	$10,400
Benralizumab	$4,700	$8,300	$11,900
Dupilumab	$6,000	$10,100	$14,300

QALY: quality-adjusted life year

Summary and Comment

The base-case findings from our analysis suggest that the use of asthma biologic agents in the studied populations provides clinical benefit in terms of gains in quality-adjusted survival over that of SoC alone. Due to high biologic treatment costs, the cost-effectiveness estimates did not meet commonly-cited cost-effectiveness thresholds. This interpretation of the incremental cost-effectiveness findings was robust to one-way and probabilistic sensitivity analyses for all biologic agents. Sensitivity analysis was also used to isolate the impact of the three main biologic agent benefits: non-exacerbation health state utility improvement alone, exacerbation reductions alone (with indirect mortality benefits), and chronic oral steroid reductions alone. The findings from this sensitivity analysis suggested that non-exacerbation health state utility improvements associated with biologic therapy are potentially the most influential benefit input on lifetime discounted cost-effectiveness, followed by exacerbation reductions and finally, the chronic oral steroid reductions. Scenario analyses suggested that the most influential scenarios were including the potential costs and benefits of biologic treatment responders (and non-responders) as well as reserving biologic treatment only in the chronic oral corticosteroid subgroup.

In conclusion, the findings of our analysis suggest that the biologic agents of focus for this review provide gains in quality-adjusted survival over standard of care alone. With the evidence available at this time, these biologic agents seem to be priced higher than the modeled benefits over a lifetime time horizon at commonly accepted cost-effectiveness thresholds. The findings were not sensitive to traditional sensitivity or scenario analyses but were most favorable in scenarios associated with long-term biologic treatment for responders or biologic initiation in the subgroup of chronic oral corticosteroid users. Comparative evidence is needed to support or refute these scenario value projections. Higher value care is more likely to be achieved through careful patient selection and continued biologic therapy for only treatment responders.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits 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. These elements are listed in table ES11 below.

Table ES11. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	None
This intervention offers reduced complexity that will significantly improve patient outcomes.	None
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	None
This intervention will significantly reduce caregiver or broader family burden.	The five biologics are all parenteral, which may impact the acceptability and long-term adherence to therapy. Four are delivered subcutaneously and one (reslizumab) is given by IV infusion. Only dupilumab is approved for self-injection. All of the other drugs require an office visit for each dose for administration by a health care professional. The requirement for office visits is potentially burdensome. In addition, the dosing schedule varies between the drugs, which may also impact long-term adherence and acceptability to patients. Dupilumab is given every two weeks, omalizumab is given every two to four weeks, mepolizumab and reslizumab are given every four weeks, and after the first three doses, benralizumab is given every eight weeks, which some patients may prefer.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Dupilumab, in particular, offers a new mechanism of action. It is the first drug to target the IL-4 and IL-13 pathways in type 2 asthma.
This intervention will have a significant impact on improving return to work and/or overall productivity.	There is limited evidence in the studies to date, but patients with severe asthma often miss school or work due to their asthma and even if present, may be less alert due to poor sleep or ongoing shortness of breath. All five biologics have the potential to improve this aspect of a patient's life.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	None

Table ES12. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	These 5 drugs are primarily intended for severe asthma that is not controlled by available therapies. The disease is life threatening and has large impacts on quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Asthma is a life-long disease and for children suffering from severe, poorly controlled asthma, the disease may impact the entire trajectory of their lives.
This intervention is the first to offer any improvement for patients with this condition.	None
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	None
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	All the biologic interventions manipulate the immune response of patients and the long-term implications of such manipulation remain unclear.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	None

Value-Based Benchmark Prices

Our value-based benchmark annual prices for the five asthma biologics are presented in Table ES13. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For all considered biologics, the discounts required to meet both threshold prices are greater than their current discount from WAC.

Table ES13. Value-Based Benchmark Prices of Asthma Biologics in the Treatment of Moderate to Severe Uncontrolled Asthma

Intervention	Annual WAC	Annual Price at $100,000 per QALY Threshold	Annual Price at $150,000 per QALY Threshold	Discount from WAC Required to Achieve Threshold prices
Omalizumab	$39,048	$9,000	$13,300	66% to 77%
Mepolizumab	$37,293	$9,200	$13,400	64% to 75%
Reslizumab	$31,637	$6,500	$10,400	67% to 80%
Benralizumab	$30,889*	$8,300	$11,900	62% to 73%
Dupilumab	$38,110‡	$10,100	$14,300	62% to 73%

*Assuming 6.5 doses per year, year-two onward since year-one has additional loading doses.

‡ Assuming 26 doses per year, year-two onward since year-one has an additional loading dose.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab in its indicated population for asthma: adults and children twelve years of age and older with uncontrolled, moderate to severe asthma in the US. We used the WAC, net price, and the three threshold prices for dupilumab in our estimates of budget impact. We did not include omalizumab, mepolizumab, reslizumab or benralizumab in our calculations since they have all already been approved and have been in use in the US marketplace for close to a year, or more.

Table ES14 illustrates the per-patient budget impact calculations, based on WAC ($38,110 per year), net price ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($14,300 per year, $10,140 per year, and $5,980 per year, respectively) compared to current treatment mix.

Table ES14. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$46,059	$38,912	$22,127	$17,945	$13,764
Current Treatment Mix*	$44,651				
Difference (Dupilumab – Current Treatment Mix)	$1,408	($5,738)	($22,524)	($26,705)	($30,887)

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*27% of target population on biologics and 73% on standard of care. Market share among biologics: reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2%, and omalizumab – 74.9%

() – Cost-saving

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $1,400 per year. Average potential budgetary impact at dupilumab's net price resulted in cost-savings of approximately $5,700 per patient annually. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug were estimated to be cost saving, ranging from approximately $22,500 per patient in savings using the annual price to achieve $150,000 per QALY to approximately $30,900 per patient in savings using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold. It is important to note that these findings are versus a population-level treatment mix of biologics and SoC. Against just SoC alone, using dupilumab will result in greater budget impact at both the per patient and the population level across the five price points (WAC, net price, prices to reach willingness-to-pay [WTP] thresholds of $50,000, $100,000 and $150,000 per QALY).

At dupilumab's WAC, 91% of the eligible population could be treated before the total budget impact exceeds the ICER annual budget impact threshold. At its net price and prices to reach the

cost-effectiveness thresholds between $50,000 and $150,000 per QALY, the total population budget impact resulted in cost-savings and the entire population could be treated.

Access and Affordability

As illustrated in the budget impact analysis, treating the entire patient population eligible for treatment with dupilumab at the net price and prices to reach commonly accepted WTP thresholds resulted in net savings. Additionally, at dupilumab's WAC, just over 90% of the entire eligible population could be treated each year without the total budget exceeding the ICER budget impact threshold. At the November 29, 2018 public meeting, the consensus among stakeholders was that uptake of dupilumab would likely not threaten access and affordability, given current market competition and dupilumab's anticipated net price for this indication. As such, ICER is not issuing an access and affordability alert at this time. However, all stakeholders should closely monitor the use of dupilumab for uptake exceeding expectations, along with any unprecedented net price increase.

Midwest CEPAC Votes

For patients ≥ 12 years with uncontrolled, moderate to severe asthma, and eosinophilic phenotype:

1. **Is the evidence adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care (ICS plus at least one additional controller medication)?**

Yes: 12 votes	No: 3 votes

For patients ≥ 12 years with uncontrolled, severe asthma, and eosinophilic phenotype:

2. **Is the evidence adequate to distinguish the net health benefit *among* mepolizumab, reslizumab, and benralizumab?**

Yes: 1 vote	***No: 14 votes***

IF NO…

3. **Is the evidence adequate to distinguish the net health benefit *between* dupilumab and these three treatments?**

Yes: 0 votes	***No: 15 votes***

4. **Is the evidence adequate to distinguish the net health benefit *between* omalizumab and these three treatments?**

Yes: 0 votes	***No: 15 votes***

5. **In the treatment of patients ≥ 12 years with moderate to severe asthma, does dupilumab offer one or more of the following potential other benefits or disadvantages compared to best usual care without biologic treatment?**

Dupilumab offers reduced complexity that will significantly improve patient outcomes.	3/15
Dupilumab will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	0/15
Dupilumab will significantly reduce caregiver or broader family burden.	6/15
Dupilumab offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	8/15
Dupilumab will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	7/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3/15

6. **Are any of the following contextual considerations important in assessing the long-term value for money of dupilumab versus best usual care without biologics?**

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/15
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12/15
This intervention is the first to offer any improvement for patients with this condition.	0/15
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	8/15
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	11/15
There are additional contextual considerations that should have an important role in judgments of the value of this intervention:	3/15

7. **Are there important and distinctive other benefits or disadvantages, or unique contextual considerations that apply to any of the other biologic treatments for their labeled population?**

Council members noted that dupilumab can be self-administered at home by the patient, whereas the other biologics in the review required an office visit for administration. Conversely, one Council member commented that while self-administration presents an opportunity for increased access, it also risks causing a decrease in adherence. Lack of adherence is not only dangerous for patients but creates significant waste in health-care spending, particularly in this case due to the high cost of the drug. Many Council members acknowledged that self-administration presents a trade-off, but all agreed the increased ease of self-administration was a net-positive for patients.

Long-term Value for Money Votes

As described in ICER's recent update to its **value assessment framework**, questions on "long-term value for money" are subject to a value vote only when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. As shown in the Evidence Report, the estimates for all five biologics exceed the higher end of the range and thus all interventions are deemed "low value" without a vote of the panel.

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on asthma biologics to policy and practice. The policy roundtable members included two patient representatives, two clinical experts, one payer, one pharmacy benefits manager, and representatives from all five manufacturers of asthma biologics. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in Section 8.3.

Manufacturers

- To provide fair value to patients and the health system, manufacturers should lower the prices of biologic therapies for asthma so that they align with the added value they bring to patients.

Plan Sponsors

- Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing excellent access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.

Payers

- Given that, to date, manufacturers have not priced biologics for asthma at a value-based level, payers are likely to offer preferential formulary status in return for lower prices. For many patients the evidence is not adequate to determine which drug would be superior as a first option, therefore it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients.

- In addition to step therapy, payers will to develop prior authorization criteria to ensure that prescriptions are covered only for appropriate patients and that use of these expensive medications is prudent.
- The process for authorization of biologic therapies for asthma should be clear and efficient for providers.
- When patients change insurance, coverage for their biologic should be continued to avoid worsening of asthma control.
- Payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their ICS or other long-acting controller medications during treatment with the biologic.
- Manufacturers, insurers, and governments should work to remove barriers to indication-specific pricing.

Specialty Societies

- Specialty societies should develop a clear definition of response to biologic therapy.
- Because of pervasive cost issues, pulmonologists, allergists and their specialty societies should advocate for prices to be better tied to the clinical benefits that drugs bring to their patients.

Researchers

- Head to head comparisons of the biologic therapies for asthma are essential.
- Better instruments to measure quality of life need to be developed.

Regulators

- The FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.
- Active comparators should be the standard in pivotal trials.

1. Introduction

1.1 Background

Background

The Centers for Disease Control and Prevention (CDC) estimates that 20.4 million Americans ages ≥ 18 years currently have asthma and an additional 6.1 million children have asthma.[1,2] 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 room visits, and 440,000 hospitalizations each year in the US.[2] The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma related mortality, and $3 billion from missed work and school.[2] There is a broad spectrum of asthma severity. Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[3]

Asthma severity is defined as intermittent or persistent, with persistent asthma subdivided into mild, moderate, and severe.[3] These categories are defined by the frequency of symptoms, lung function, and frequency of exacerbations requiring OCS. 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 medication (leukotriene inhibitor/theophylline) to maintain control.[32] Patients with severe asthma commonly have daily symptoms, awaken at night due to symptoms, have significant limitations in normal activities and an FEV_1 <60% of the normal predicted volume. When asthma is well-controlled, patients have symptoms ≤2 times per week, nocturnal awakening ≤2 times per month, no interference with normal activity, and an FEV_1 >80% of predicted.[3]

Asthma prevalence and severity is greater in Black Americans and in low income, urban populations leading to more hospitalizations and death from asthma.[33-35] Evidence suggests that most of the disparities are due to social determinants of health (education, environmental exposures, psychosocial stressors, access to health care) rather than biologic factors.[36-40]

There are a number of treatments available for asthma, and a stepped care approach is recommended.[3] Short-acting beta agonists (SABAs), 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 LABAs. 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 frequent or 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.[41] Additional therapies for severe asthma include leukotriene inhibitors, theophylline, omalizumab, mepolizumab, reslizumab and benralizumab. Treatment is progressive from Step 1 (SABA as needed), Step 2 (addition of controlled medication, typically low does ICS) to Step 3 (low dose ICS + LABA) Step 4 (medium dose ICS +LABA) to Step 5 (high dose ICS + LABA with consideration of OCS, omalizumab in the subgroup of patients with allergic asthma, or one of the three drugs targeting the IL-5 pathway (mepolizumab, reslizumab and benralizumab) in patients with eosinophilic asthma).[42]

Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells.[4] These cells secrete IL-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[5,6] Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma.[43,44]. The medications evaluated in this review target specific components of these pathways and may be more effective in specific asthma patient subgroups.

Monoclonal antibody therapies

This assessment will consider 5 monoclonal antibodies that affect the pathways involved in either the allergic or type 2 inflammatory phenotypes of asthma. The drugs, dosing, their mechanism of action, and their FDA indications for asthma are summarized in Table 1.1 below. Omalizumab is a monoclonal antibody to IgE, which is indicated for the treatment of patients with moderate to severe asthma with the allergic phenotype described above. Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway either with monoclonal antibodies to IL-5 itself (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab). Dupilumab is a monoclonal antibody to the IL-4 receptor alpha, which modulates both the IL-4 and IL-13 pathways.

Table 1.1. Monoclonal Antibody Therapies for Type 2 Inflammation in Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®, Genentech)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens[7]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[8]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[9]
Benralizumab (Fasenra™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[10]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	Age ≥ 12 years with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma[11]

There are important differences in the indications for each of the drugs even though each drug targets some part of the type 2 inflammatory phenotype (Table 1.1). The covered ages in the pediatric population varies across the five agents from ≥ 6 years for omalizumab, to ≥ 12 years for mepolizumab, benralizumab and dupilumab, to ≥ 18 years for reslizumab. Omalizumab is the only drug approved for the allergic asthma, while the other four drugs are approved for asthma with the eosinophilic phenotype. Finally, two of the drugs are approved for moderate to severe asthma (omalizumab, dupilumab), while the other three are approved for severe asthma only (mepolizumab, reslizumab, benralizumab). It is also worth noting that dupilumab is the only one of the five biologics that is approved for self-administration. The other four require administration by a health professional.

There may be additional benefits for patients suffering from other conditions linked to type 2 inflammation. Three of the 5 agents carry FDA indications for conditions other than asthma. Omalizumab is indicated for chronic idiopathic urticaria. Mepolizumab is indicated for eosinophilic granulomatosis with polyangiitis, and dupilumab is indicated for moderate to severe atopic dermatitis.

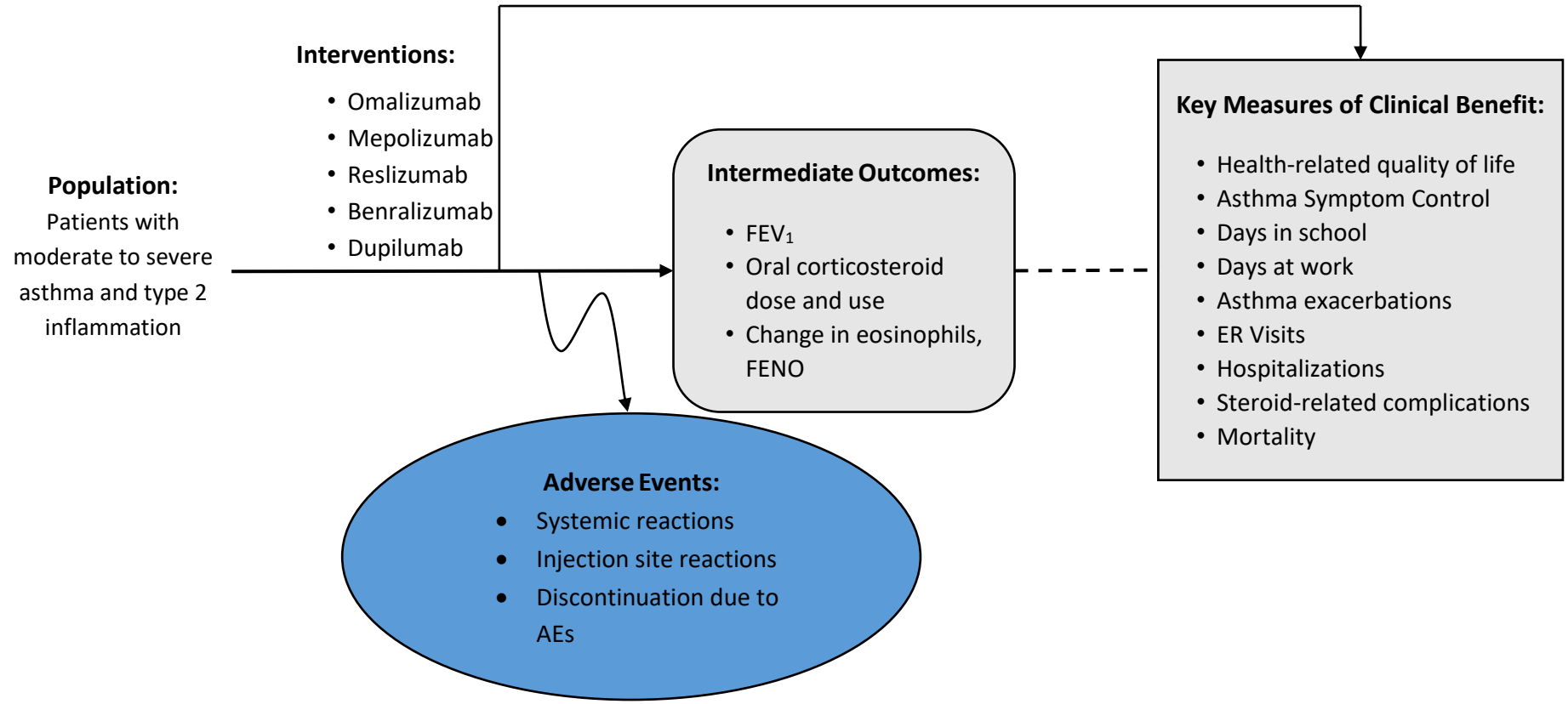
1.2 Scope of the Assessment

The scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials as well as high-quality systematic reviews and high-quality cohort studies. Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis are available in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1 on the following page.

Figure 1.1. Analytic Framework: Asthma Management with Biologic Therapies



Note: AEs: adverse effects; FENO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; SAEs: severe adverse effects

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., Oral corticosteroid dose), and those within the squared-off boxes are key measures of benefit (e.g., Health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[45]

Populations

The population of focus for the review is adults and children ages six years and older with moderate to severe, uncontrolled asthma and evidence of type 2 inflammation and/or allergic asthma. The population is intentionally broad to capture the indicated populations for all of the biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma. However, for each biologic, we focus primarily on the evidence in its labeled indication. Severe asthma is typically defined as asthma that requires either oral corticosteroids for >50% of the year or the combination of high-dose inhaled corticosteroids and a long-acting beta-agonist or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[32] We recognize that the definitions of both moderate and severe asthma have evolved over time and differ slightly in the most recent GINA and ERS/ATS guidelines.[32,42] Uncontrolled asthma is typically defined by at least one of the following: frequent exacerbations (2+ bursts of oral steroid therapy lasting at least 4 days in the past year); at least one serious exacerbation (hospitalization, ICU stay or mechanical ventilation) in the past year; airflow limitation (FEV_1 <80% predicted); or poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test < 20).[32] Similarly, we recognize that the definition of an asthma exacerbation varies across the trials. All individuals should be treated with high-dose inhaled corticosteroid therapy and at least one additional controller medication (e.g., long-acting beta-agonists, long-acting muscarinic agents, leukotriene agonists, theophylline, oral corticosteroids).

Many of the trials excluded participants who were on long-term OCS, although some of the trials allowed maintenance OCS use. Finally, some of the trials included only individuals who were dependent on long-term oral corticosteroids for asthma control, which is a subgroup of individuals with more severe asthma. In addition to looking at overall outcomes, we also summarized data for the subgroup of patients who require long-term oral corticosteroid therapy to maintain control of their asthma.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The interventions of interest will be one of the following added to daily inhaled corticosteroid therapy plus at least one additional controller therapy:

- Omalizumab 75-375 mg by subcutaneous injection once every two or four weeks
- Mepolizumab 100 mg by subcutaneous injection once every four weeks
- Reslizumab 3 mg/kg by intravenous infusion once every four weeks
- Benralizumab 30 mg by subcutaneous injection once every four weeks for three doses; then every eight weeks
- Dupilumab 200 mg or 300 mg by subcutaneous injection once every two weeks

Comparators

The comparator of interest is standard of care (daily inhaled corticosteroids plus at least one additional controller therapy).

Outcomes

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

- Symptom scale/quality of life including nocturnal symptoms and impact on daily activities such as the Asthma Quality of Life Questionnaire (AQLQ)
- Asthma control assessed by standard questionnaires: Asthma Control Questionnaire or Asthma Control Test (ACQ or ACT)
- Clinically significant asthma exacerbations (3+ days of systemic corticosteroids with or without ER visit or hospitalization)
- Asthma-related hospitalizations and emergency room visits
- Mortality (Asthma-specific and total)
- Use of oral steroids including a reduction in dose for those on chronic oral steroids
- Forced expiratory volume in one second (FEV_1)
- Absence from school
- Absence from work
- Adherence
- Harms (serious adverse events, injection site reactions, infections)

Timing

Evidence on intervention effectiveness and harms were derived from studies of at least 24 weeks duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings, but the focus will be outpatient use of the five therapies.

1.3 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.[32]

Moderate asthma is defined as asthma that is controlled with low dose ICS plus LABA.[42]

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)[32]

Eosinophilic inflammation is typically defined as a blood eosinophil level ≥150 cells/µL at initiation of therapy or ≥300(cells/µL in the prior 12 months, though sometimes as blood eosinophil level ≥400 cells/µL.

Asthma Control Questionnaire (ACQ) scores range from zero to six with higher scores indicating worse control and a change of 0.5 points being the minimal clinically important difference. The ACQ is a seven-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points.

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

Asthma Quality of Life Questionnaire (AQLQ): The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points.

FEV_1: The FEV_1 is the maximal volume of air that a person is able to blow out in one second. It is a measure of airflow obstruction in the lungs with lower values representing greater obstruction.

1.4 Insights Gained from Discussions with Patients and Patient Groups

The most important insight gained from speaking with patients was their heartfelt desire to be able to perform their day to day tasks of living – to get back to their usual activities of daily living. They want to be back at work and back at school without limitations. Symptom relief, asthma control, and quality of life matter much more to them than a reduction in asthma exacerbations. These include the ability to exercise and the ability to get a good night's sleep, uninterrupted by asthma symptoms. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

The Asthma and Allergy Foundation of America shared results from their survey of 805 Americans living with asthma including 185 with severe, uncontrolled asthma.[12] The two most important factors for choosing a therapy for both groups were effectiveness and then cost. However, effectiveness was the far more important factor for patients surveyed. An average of 82% responded that effectiveness was a key criterion while an average of 52% cited cost as a key criterion.

Adherence with therapy was also raised as an issue. The top three reasons for non-adherence were related to cost: inability to afford treatment, treatment too expensive, and lack of insurance coverage for treatment.[12]

In addition, the Asthma and Allergy Foundation of America's survey showed that patients had limited knowledge about biologic treatments. An average of only 10% of those surveyed were knowledgeable about biologic treatments. This suggests that biologics are not widely discussed nor prescribed by clinicians.[12]

1.5 Potential Cost-Saving Measures in Asthma

As described in its Final Value Assessment Framework for 2017-2019, ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by biologic therapy for moderate to severe asthma (e.g., reduction in exacerbations, ER visits, and hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of asthma beyond the potential offsets that arise from a new intervention.

ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

Stakeholders have not identified any such services to date.

The Choosing Wisely statement from the **American Academy of Allergy, Asthma & Immunology** includes the following:

Don't diagnose or manage asthma without spirometry.

"Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore, spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment." [13]

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for biologic therapies for treatment of asthma associated with type two inflammation, we reviewed publicly available 2018 coverage policies and formularies for Midwestern state Medicaid programs (Missouri and Illinois), regional commercial plans (Blue Cross Blue Shield Kansas City, WellCare IL, and Aetna Better Health IL), and major national commercial plans, including Aetna and Cigna. We surveyed each plan's coverage policies for the five biologics in this review: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. No coverage policies were found for dupilumab as a treatment for asthma, because at the time of this publication it has only just been approved by the FDA as an asthma treatment.

Across most of these policies, coverage of these drugs required one to three severe exacerbations in a three to twelve-month period, despite the continued use of a moderate to high-dose inhaled cortical steroid (ICS) and another controller therapy such as a long-acting beta agonist (LABA) or leukotriene receptor antagonist (LTRA). Most policies defined a "severe exacerbation" as one that required multiple days of systemic corticosteroids use (either oral, intravenous, or subcutaneous) and/or an ER visit, hospitalization, or mechanical ventilation.

More specifically, for the four biologics approved by the FDA, all had a non-preferred status in both MO and IL Medicaid programs. Missouri requires the first dose for all four biologics be prescribed by a specialist and the patient have symptoms uncontrolled with continued use of an ICS and another controller therapy. The state also requires that the patient visited the ER for an asthma exacerbation in the past 45 days.[46] Specific criteria for Illinois' Medicaid program could not be found.

Among the three regional commercial plans surveyed, none covered any of these biologics except for WellPoint IL, which covered omalizumab.[47] No specific formulary information could be found.

On the national level, Aetna and Cigna each covered all four of the FDA approved biologics in this review—both payers requiring step therapies and previous exacerbations necessitating an ER or urgent care visit, hospital admission, or high dose injectable or oral cortical steroids. Coverage specifics for these national plans are detailed below in Table 2.1.

Table 2.1. Representative National Private Payer Policies for Omalizumab, Mepolizumab, Reslizumab, and Benralizumab[48-53]

	Aetna	Cigna
Omalizumab		
Tier	4	3
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Requirements	≥ 3 exacerbations in the past 3 months despite use of ICS	Uncontrolled symptoms despite use of ICS and controller therapy
Reauthorization Required	Yes, after 3 months	Yes, after 12 months
Mepolizumab		
Tier	5	4
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Requirements	≥ 2 exacerbations in past 12 months despite use of high-dose ICS and additional controller therapy	≥ 2 exacerbations or 1 hospitalization in the past 12 months despite use of high-dose ICS and an additional controller therapy OR inadequate control with daily oral corticosteroids in the last 12 months
Reauthorization Required	Yes	Yes, after 12 months
Reslizumab		
Tier	3	
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Criteria	≥ 1 exacerbation in past 12 months despite use of high-dose ICS and oral corticosteroids	≥ 2 exacerbations in the past 12 months OR ≥ 1 exacerbation requiring hospitalization in the past 12 months, despite use of high-dose ICS and an additional controller therapy
Reauthorization Required	Yes	Yes, after 12 months
Benralizumab		
Tier	3	
Prior Authorization	Yes	N/S
Step Therapy	Yes	N/S
Eligibility Criteria	≥ 2 exacerbations requiring systemic corticosteroid treatment in the past 12 months, despite use of high-dose ICS and an additional controller therapy	N/S
Reauthorization Required	Yes	N/S

2.2 Clinical Guidelines

The U.S. Department of Health and Human Services, National Institutes of Health, and National Heart, Lung, and Blood Institute

The U.S. Department of Health and Human Services (HHS), National Institutes of Health (NIH), and National Heart, Lung, and Blood Institute (NHLBI) jointly released clinical guidelines for the diagnosis and treatment of asthma. The most updated guidelines, released in 2007, specify four components to care after diagnosis: assessment and monitoring, education, controlling environmental factors and comorbid conditions, and medications. These four components, as well as diagnostic criteria, are summarized below.[54]

Diagnosis: Clinicians must evaluate symptoms of recurrent airflow obstructions, ruling out other possible causes, such as a heart condition. Common symptoms of asthma include: wheezing, coughing, and difficulty breathing, with symptoms potentially worsening at night, during one's menstrual cycle, and/or with exercise, presence of allergens, changes in weather or strong emotional expression. The presence of multiple symptoms may suggest that asthma is probable, but clinicians must use spirometry in patients at or above the age of five to establish an asthma diagnosis. Spirometry can demonstrate whether the airway is obstructed and if the obstruction is at least partially reversible.

Four Components to Care

I. **Assessment and Monitoring:** Clinicians are instructed to use the severity classification chart to determine initial treatment, keeping in mind multiple measures of impairment and risk. Asthma manifests in different ways and these measures may or may not correlate to each other and may respond differently to the same treatments. The guidelines warn that asthma is highly variable over time and requires consistent periodic monitoring, recommending that doctors see patients at two to six-week intervals while gaining control of symptoms, at least every six months to evaluate care management, and every three months if a step-down therapy is being considered.
II. **Education:** Guidelines emphasize teaching patients how to self-assess their symptoms and avoid environmental factors that exacerbate the condition. Clinicians are advised to work with patients to create a "written asthma action plan" so patients can agree on treatment goals and understand treatment protocol. Moreover, the guidelines state that clinicians should take special care to review the differences between long-term control and quick-relief medication and what medications and/or interventions each involves. Clinicians also must ensure that patients understand how to correctly use their inhalers and/or devices.
III. **Control Environmental Factors and Comorbid Conditions:** Clinicians must evaluate patients for environmental sensitivities and symptom triggers and advise patients on how to avoid common irritants. The guidelines recommend using skin or in vitro testing to assess

sensitivity to indoor allergens, in patients with persistent asthma; and when there is clear evidence of a relationship between exposure to a particular allergen and exacerbated symptoms, allergen immunotherapy should be considered. The guidelines also stress the necessity of treating comorbid conditions that could exacerbate symptoms, highlighting—allergic bronchopulmonary aspergillosis; gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis and sinusitis, and stress or depression—noting that asthma control may improve by treating these conditions.

IV. **Medications:** The last component to care is medication. The guidelines divide asthma medications into long-term control medications and quick-relief medications. Patients with persistent asthma require long-term control medication in addition to quick-relief medications for acute exacerbations. These clinical guidelines outline a stepwise approach (Step 1 being the minimum medication protocol and Step 5 being the heaviest medication protocol) to identifying appropriate medications for asthma patients.
    a. **Quick relief medications:** These medications should be used to treat acute exacerbations.
        i. **Short-acting beta agonists (SABAs):** Step 1 treatment involves administering SABAs, such as albuterol, for relief of mild intermittent asthma. If SABAs are used more than twice a week for symptom relief, this indicates uncontrolled asthma and additional therapies should be considered.
        ii. **Anticholinergics** can be used as an alternative to SABAs if SABAs are not tolerated by the patient.
    b. **Long-Term Control Medications:** Patients suffering persistent symptoms, despite the use of SABAs or anticholinergics, should consider daily long-term control medications. The guidelines outline the most common medications and broad step-therapy guidance, which is listed below:
        i. **Corticosteroids**, most often as an Inhaled Corticosteroids (ICS), are the most consistently effective treatment for patients with persistent asthma at Steps 2 and above. Clinicians are advised to begin long-term therapy with ICS and then reevaluate control. Oral corticosteroids (OCS) are used as a Step 6 treatment for patients with severe persistent asthma.
        ii. **Cromolyn sodium and nedocromil** are an alternative to corticosteroids for patients requiring Step 2 care but should only be used if corticosteroids do not provide control.
        iii. **LABAs** (salmeterol and formoterol) are used in combination with ICS for long-term control of moderate to severe persistent asthma in patients ages five and above requiring Step 3 care or higher, and patients under the age of five requiring Step 4 care or higher. Of all the available controller medications, the guidelines highlight LABAs as the preferred adjunctive therapy for patients at or over the age of 12.

iv. **Leukotriene modifiers** include LTRAs (montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). LTRAs are alternative therapies for patients with mild persistent asthma requiring Step 2 care, often used in conjunction with ICS. However, if the patient is at or over the age of 12, LABAs should be considered as an alternative treatment first. Zileuton is another alternative therapy for adults with mild, persistent asthma, but is not preferred.

v. **Immunomodulators** are used as additional therapy for patients at or over the age of 12 with moderate to severe, persistent asthma requiring Step 5 or 6 care, who also have sensitivities to applicable allergens. These guidelines specifically name omalizumab as one of these treatments.

vi. **Methylxanthines** (including theophylline) are an alternative, but not preferred, adjunctive controller therapy for patients requiring Step 2 care at or above the age of five.

c. The guidelines advise that clinicians consistently monitor level of asthma control and adjust as needed. If asthma is well-controlled for three months, a step-down therapy should be considered. As therapies are being stepped up or down, clinicians should see patients every one to six weeks.

National Institute for Health and Care Excellence (NICE)

We also reviewed clinical guidelines from the National Institute for Health and Care Excellence (NICE). Recommendations were similar to those discussed above, aside from the following key differences:

- **Anticholinergics** are not advised for mild intermittent asthma. A long-acting muscarinic receptor antagonist may be used as an additional therapy for patients at or above the age of 17 if asthma remains uncontrolled on ICS with a LABA, with or without an LTRA.
- **LTRAs and LABAs:** If asthma is uncontrolled with first-line maintenance therapy on ICS, NICE recommends offering a LTRA in addition to ICS and reevaluating treatment after four to eight weeks. If asthma remains uncontrolled, patients may be offered a LABA in combination with ICS, and LTRA treatment may be continued or discontinued depending on the response to treatment.
- **Maintenance and reliever therapy (MART)**, involving the combination of low maintenance ICS dose and a LABA with a fast-acting component in a single inhaler, may be used if asthma is uncontrolled on ICS with a LABA, with or without an LTRA.[55]

These guidelines make clear that the biologics evaluated in this report are one piece of a comprehensive treatment plan that includes close clinician monitoring and assessment, control of patient's environment and comorbidities, and patient engagement and adherence to his/her full treatment plan.

American Thoracic Society (ATS) and European Respiratory Society (ERS)

In 2013, a task force supported by the American Thoracic Society (ATS) and European Respiratory Society (ERS) produced clinical guidelines on the diagnosis and treatment of severe asthma in children and adults. These guidelines, summarized below, outline a stepwise treatment plan that is similar to that recommended by the HHS, NIH, and NHLBI.

Diagnosis: The ATS-ERS task force recommends diagnosis in children by clinical criteria along. In adults, sputum eosinophil counts should be evaluated in addition to clinical criteria only in centers experienced in using this technique. Exhaled nitric oxide should not be used to guide therapy.

Treatment: Severe asthma should be controlled with a combination of high dose inhaled corticosteroids, beta-agonists, leukotriene receptor antagonists, and/or other controller medications.

- **Oral and inhaled corticosteroids:** Because severe asthma necessarily involves corticosteroid insensitivity, OCS are often required in addition to ICS to maintain control of asthma symptoms. Higher than average doses of ICSs may be used in patients with moderate to severe asthma. However, it is noted that systemic corticosteroid use can lead to serious long-term adverse effects.
- **Beta-agonists:** Step-wise increases in the dose of ICS together with a LABA are recommended if asthma is not controlled with an ICS alone. Patients with severe asthma may also receive a LABA in combination with an as-needed SABA.
- **Leukotriene pathway modifiers:** Adding a leukotriene receptor antagonist or synthesis inhibitor to ICS has been shown to improve lung function in adults with moderate to severe asthma. However, montelukast has been shown to be less effective than LABAs when added to ICS.
- **Other therapies:** A therapeutic trial of omalizumab is recommended in adults and children with severe allergic asthma. In moderate asthma, theophylline may be added to an ICS to improve asthma control. Tiotropium bromide, a long-acting muscarinic antagonist, has also been shown to improve lung function in adults whose asthma was not controlled on moderate- to high-dose ICS with or without a LABA.

Global Initiative for Asthma

The Global Initiative for Asthma (GINA) Science Committee meets biannually alongside the ATS and ERS international conferences to conduct a systematic review of the asthma literature and produce revised clinical guidelines for evaluation and treatment of asthma. Recommendations from the most recent version of the report, updated in 2018, are summarized below. The GINA guidelines outline a continuous asthma management cycle emphasizing assessment, pharmacological and non-pharmacological treatment, and review.

Assessment: Patients with asthma will present with respiratory symptoms such as wheezing, shortness of breath, cough, and chest tightness, that are often worse at night or in the early morning and may be triggered by environmental factors, exercise, or viral infections. The presence of these symptoms suggest that a patient may have asthma, but a diagnosis should be confirmed by a detailed history and examination for asthma and spirometry. Asthma control should then be assessed by symptom control, treatment issues, and comorbidities.

Treatment: A step-wise approach is recommended to control asthma symptoms and minimize future risk. Step 1 treatment should be initiated with an as-needed SABA and low dose ICS may be considered as a controller. If asthma remains uncontrolled on step 1 treatment, low dose ICS should be administered. An LTRA or low dose theophylline may be used as an additional controller. Allergen immunotherapy may also be considered if is there is a clear relationship between exacerbations and exposure to a specific allergen. Step 3 treatment involves addition of an LABA to low dose ICS. ICS dosage may be increased at this point, if needed, and formoterol may be considered as an alternative reliever medication. Medium or high dose ICS in addition to a LABA is recommended for step 4 treatment, and tiotropium may be considered as a controller option. If severe asthma remains uncontrolled on step 4 therapy, the patient should be referred for add-on treatment, such as an anti-IgE or anti-IL5 biologic. Low dose OCS may also be added as a controller.

Review: Before stepping up treatment, clinicians should check for issues such as improper use of an inhaler, poor adherence to medication, or environmental factors, and confirm that the diagnosis is correct. Clinicians may consider stepping down treatment if symptoms remain controlled for three months and there is low risk for exacerbations. However, stopping ICS treatment is not recommended.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of the five biologics added to standard of care (SoC) versus SoC alone, we abstracted evidence from RCTs of individuals ages six years and older with moderate to severe allergic asthma or eosinophilic asthma. The comparator treatment for each intervention of interest included SoC treatment with ICS and at least one additional controller agent. Our review focused on clinical benefits (i.e., asthma exacerbations, ED visits, hospitalizations, quality of life (AQLQ, ACQ, SGRQ) as well as potential harms (severe adverse events, adverse events leading to discontinuation of therapy). We also summarized intermediate markers of interest including change in FEV_1 and blood eosinophil levels.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab for moderate to severe asthma follow established best methods.[56,57] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58,59] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Eligibility criteria described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2 and A3.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and resolved any issues of disagreement through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction Strategy

Data were extracted into evidence tables (Appendix Tables D1-D6).

Data extraction was performed in the following steps:

1. Two reviewers extracted information from the full articles.
2. Extracted data was reviewed for logic, and data were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[60]

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "omalizumab," "mepolizumab," "reslizumab," "benralizumab," and "dupilumab." We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Summary of Evidence Base

The studies are summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence tables are presented in Appendix Tables D1-D6. Relevant data include those listed in the data extraction section. Important differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality are noted in the text of the report.

Synthesis of Results

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. We used the estimates from two Cochrane systematic reviews and meta-analyses for omalizumab, mepolizumab, reslizumab and benralizumab.[14,15] We identified only one relevant trial for dupilumab for each of the outcomes (reduction in exacerbations, improvements in quality of life, reduction in oral corticosteroid dose), so no meta-analysis needed to be performed. We performed our own meta-analysis for outcomes that were not assessed in the Cochrane reviews (discontinuation due to AEs for omalizumab; injection site reactions for mepolizumab, reslizumab, and Benralizumab).

We defined a population that was similar enough in baseline characteristics to conduct a network meta-analysis: patients with baseline eosinophil counts ≥ 300, at least 2 exacerbations in the prior year, and a baseline ACQ score ≥ 1.5. We appreciate the cooperation of the manufacturers who shared data for this subgroup to inform our report. The inputs and methods used for the analysis are reported in Appendix D.

3.3 Results

The results are organized by outcome and then by drug within outcome in the order of FDA approval. For each drug, we only included trials that randomized patients to the FDA approved dose and formulation of the drug with at least 24 weeks follow-up. For example, trials of the IV formulation of mepolizumab are not included because the FDA approved formulation is SC. For summary estimates, we used the 2014 Cochrane Review for omalizumab[14] and the 2017 Cochrane Review for mepolizumab, reslizumab, and benralizumab.[15] For mepolizumab, reslizumab, and benralizumab we only used the results for patients with eosinophilic asthma to match the FDA indications for those three drugs.[8-10]

There is significant heterogeneity in the FDA indications for the five drugs: allergic versus eosinophilic asthma and starting ages of 6, 12, or 18 years. This is reflected in the differences in the inclusion criteria for the trials (Table 3.1 below and Appendix Table D2), although not always in the characteristics of the patients in the clinical trials (Appendix Table D1). For example, across the clinical trials, approximately 60% of the participants were female and their baseline AQLQ score was approximately 4.1. Among the trials that enrolled both patients using and not using OCS, the proportion on OCS was approximately 17%. However, the patients in the omalizumab trials were somewhat younger (approximately 42 years vs. 48 for the other trials), which reflects the epidemiology of allergic asthma, which tends to be in patients younger than those with severe eosinophilic asthma. In addition, the annualized exacerbation rates in the placebo groups of the trials of mepolizumab and reslizumab (~2.1 per person year) were higher than those observed in the placebo groups of the trials of the other 3 drugs (~1.1 per person year).

Table 3.1. Inclusion Criteria Heterogeneity Among the Clinical Trials

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Asthma Severity	Moderate to severe	Severe	Moderate to severe	Severe	Moderate to severe
Exacerbation History (past 12 months)	-	≥2	≥1	≥2	≥1
Allergy Required	+	-	-	-	-
IgE level	30-700 IU/mL	-	-	-	-
Eosinophil Level (cells/µl)	-	≥150 at initiation or ≥300 in past 12 months	≥400	Any (stratified < vs. ≥300 at enrolment)	Any (690/1638 patients with ≥300)
Standard of Care Therapy	Medium to high dose ICS Secondary controllers allowed but not required	High dose ICS With a secondary controller medication	Medium to high dose ICS With or without another controller drug	Medium to high dose ICS With LABA	Medium to high dose ICS With LABA
Use of maintenance OCS allowed	Yes	Yes	Yes	Yes	No

ICS: inhaled corticosteroids, LABA: long-acting beta2-adrenergic agonist, OCS: oral corticosteroids, SoC: standard of care, - : not required

Another important difference seen in row 2 of Table 3.1 is that the trials of both omalizumab and dupilumab enrolled patients with both moderate and severe asthma, while the trials of the 3 IL-5 drugs (mepolizumab, reslizumab, and benralizumab) restricted their studies to patients with severe asthma. This is mirrored in the FDA indications for the 5 drugs.

In addition, the definition of an exacerbation differed between studies (Table 3.2) in part due to changes in the guidelines used to design the pivotal trials for asthma biologics. The 1997 National Heart, Blood and Lung Institute (NHLBI) Asthma guideline, which focused on level of asthma severity, was used to inform the design of the Xolair pivotal trials.[61] However, other asthma biologics, all of which were approved after 2015, based their pivotal trials on the more recent 2007 NHLBI Asthma and Global Initiative for Asthma (GINA) guidelines which focus on asthma control.[42,54]

Table 3.2. Differences in the Definition of an Asthma Exacerbation Among the Clinical Trials

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab[62,6352,5351,5249,50]	Dupilumab
Exacerbation defined by: Doubling ICS dose	+	-	+	-	-
OCS use	+	+	+	+	+
ED visit or hospitalization	-	+	+	+	+

ED: emergency department, ICS: inhaled corticosteroids, + : met definition, - : not required, OCS: oral corticosteroids

Because of these differences, we did not think it was appropriate to perform an NMA across the trials as our primary analysis. We did perform an exploratory NMA in the subgroup of patients with high eosinophil counts and at least two exacerbations in the prior year, because this group was more homogeneous and several trials reported that their biologic therapy was more effective in patients with eosinophil counts ≥ 300 cells/µL.[16,19,64]

Study Selection

Details of the search criteria are described above. The PRISMA flow diagram is Appendix Figure A1.

Quality of Individual Studies

Appendix Table D3 summarizes the quality of the included randomized trials. We judged that the trials met all criteria and were thus judged to be of good quality. Comparable groups were 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 an intention to treat analysis was used as the primary analysis.

Clinical Benefits

Reduction in Exacerbation Rates Requiring Systemic Steroids

As noted above, there were no head to head randomized or observational trials of the five monoclonal antibodies. The summary estimates from the Cochrane meta-analyses[14,15] for each of the drugs are summarized in Table 3.3 below in addition to the estimates for dupilumab from the pivotal trial.[16-18] As can be seen in the Table, all five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics.

For instance, the relative rates have been shown to be consistently lower (greater efficacy) for each of the drugs in populations with higher baseline eosinophil counts.[16-20] If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table 3.3.

Table 3.3. Rate Ratio for Asthma Exacerbations Requiring Steroid Therapy

Treatment	Rate Ratio (95% CI)
Omalizumab	0.52 (0.37-0.73)
Mepolizumab	0.45 (0.36-0.55)
Reslizumab	0.43 (0.33-0.55)
Benralizumab	0.59 (0.51-0.68)
Dupilumab 200 mg	0.44 (0.34-0.58)
Dupilumab 300 mg	0.40 (0.31-0.53)

Measures of Health-Related Quality of Life and Asthma Control

The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is even more important to patients. They want to be able to go to work and school, exercise, and sleep through the night. The measures below attempt to quantify patients' quality of life.

The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points. The average AQLQ score prior to therapy in the studies was close to four in across all of the studies.

Table 3.4. Mean Difference in AQLQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	0.26 (0.05-0.47)
Mepolizumab	NR
Reslizumab	0.28 (0.17-0.39)
Benralizumab	0.23 (0.11-0.35)
Dupilumab 200 mg	0.29 (0.15-0.44)
Dupilumab 300 mg	0.26 (0.12-0.40)

AQLQ: Asthma Quality of Life Questionnaire, NR: not reported

As can be seen in Table 3.4 above, the average improvement for four of the drugs compared with placebo is modest and none of them reach the minimally important difference, although all were statistically significant. The trials of mepolizumab using the FDA approved SC formulation did not report AQLQ outcomes data, though they did report it for the IV formulation. The AQLQ scores in Table 3.4 are average changes across all participants, some of whom had large improvements, and

some had no improvement at none at all. As with the estimates for asthma exacerbations, the change in AQLQ estimates for each drug in Table 3.4 come from different populations, so comparisons between drugs are highly uncertain due to potential selection bias. This caveat applies to all of the Tables 3.3 through 3.10 but will not be repeated for each outcome.

The ACQ is a 7-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points. The average ACQ score prior to therapy in the studies was close to 2.5 in across all of the studies (see Appendix Table D1) except for the INNOVATE study of omalizumab (mean ACQ 3.9)[65] and the DREAM study of mepolizumab (mean ACQ 4.2).[66]

Table 3.5. Mean Difference in ACQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	NR
Mepolizumab	-0.42 (-0.56 to -0.28)
Reslizumab	-0.27 (-0.36 to -0.19)
Benralizumab	-0.23 (-0.34 to -0.12)
Dupilumab 200 mg	-0.39 (-0.53 to -0.25)
Dupilumab 300 mg	-0.22 (-0.36 to -0.08)

ACQ: Asthma Control Questionnaire

As with the AQLQ, the improvements in the ACQ compared with placebo were clinically modest, but statistically significant for the four drugs that reported this outcome in randomized trials (Table 3.5).

Some of the trials of mepolizumab also reported changes in the SGRQ. The SGRQ is a 50-item questionnaire focusing on overall health, daily life, and perceived well-being. It is scored from 0 to 100 with higher numbers representing greater limitations. The minimally important difference is the four points. The SGRQ has been used in COPD but has been extensively validated in patients with asthma.[21-25] The summary estimate for mepolizumab compared with placebo was -7.40 points (95% CI: -9.50 to -5.29). By this measure, the average patient treated with mepolizumab had a clinically meaningful improvement in quality of life, even though this was not observed with the ACQ or AQLQ in these trials.

Surrogate markers of response

Several surrogate markers were reported in the majority of trials.

Pre-Bronchodilator FEV_1: The forced expiratory volume in one second (FEV_1) is a measure of obstruction to the flow of air in the lungs. When asthma is under poor control, the FEV_1 is lower than when it is under good control. All of the drugs significantly improved FEV_1 compared with

placebo (Table 3.6 below), although the magnitude of the improvement appeared to be somewhat smaller for omalizumab compared to the other four biologics. This may represent differences in the patient populations studied, particularly given that omalizumab is indicated for allergic asthma, while the other drugs are indicated for eosinophilic asthma.

Table 3.6. Mean Difference in Pre-Bronchodilator FEV_1 Between Treatment and Placebo

Treatment	Difference, L (95% CI)
Omalizumab	0.06 (0.02-0.10)
Mepolizumab	0.10 (0.01-0.18)
Reslizumab	0.12 (0.08-0.16)
Benralizumab	0.13 (0.08-0.19)
Dupilumab 200 mg	0.14 (0.08-0.19)
Dupilumab 300 mg	0.13 (0.08-0.18)

FEV_1: forced expiratory volume in one second

Blood Eosinophil Levels: Blood eosinophil levels are a marker of type 2 inflammation and are explicitly targeted by three of the drugs (mepolizumab, reslizumab, and benralizumab). The changes in blood eosinophils were not reported for omalizumab and were markedly greater for reslizumab than for the other three drugs reporting changes in eosinophil levels (Table 3.7 below). Despite having the greatest reductions in blood eosinophils, reslizumab did not have the greatest improvements in quality of life measure or improvements in FEV_1, though it did have the greatest reduction in asthma exacerbations. The inclusion criteria for the trials of reslizumab required an eosinophil count ≥ 400 cells/µL, which led to an average starting eosinophil count for the reslizumab trials (655 cells/µL) that was much higher than that for the other trials (300-500 cells/µL). This may explain in part the larger absolute decrease in eosinophil counts with reslizumab, but this does not appear to predict greater improvements in quality of life nor markedly greater reductions in asthma exacerbations.

Table 3.7. Mean Difference in Blood Eosinophil Levels Between Treatment and Placebo

Treatment	Difference, cells/µL (95% CI)
Omalizumab	NR
Mepolizumab	-170 (-228 to -110)*
Reslizumab	-477 (-499 to -454)
Benralizumab	-105 (-116 to -93)
Dupilumab 200 mg	-129 (-192 to -66)
Dupilumab 300 mg	-129 (-193 to -65)

* This is for IV dosing. Not reported for SC dosing.

Harms

All five drugs were well tolerated. As can be seen in Table 3.8 below, the risk for serious adverse events was lower in the active drug group than the placebo group for all five drugs, with the

exception of the 300 mg dose of dupilumab. The reductions were statistically significant for both omalizumab and mepolizumab. This likely reflects a reduction in asthma-related events.

Table 3.8. Risk Ratio for Serious Adverse Events

Treatment	Risk Ratio (95% CI)
Omalizumab	0.72 (0.57-0.91)
Mepolizumab	0.63 (0.41-0.97)
Reslizumab	0.79 (0.51-1.22)
Benralizumab	0.80 (0.60-1.06)
Dupilumab 200 mg	0.93 (0.59-1.47)
Dupilumab 300 mg	1.03 (0.67-1.61)

There were no differences in withdrawals due to adverse events with omalizumab compared with placebo. There were trends towards greater drug discontinuation rates due to adverse events for benralizumab (Table 3.9 below) and a significant increase in drug discontinuation rates for the 300 mg dose of dupilumab. However, there was a significant reduction in discontinuation due to adverse events for dupilumab at the 200 mg dose. Either these are chance findings, or the 300 mg dose causes more adverse events that are bothersome to patients than the 200 mg dose. For the other two drugs (mepolizumab, reslizumab), there were non-significant trends towards a lower rate of drug discontinuation due to adverse events.

Table 3.9. Risk Ratio for Adverse Events Leading to Drug Discontinuation

Treatment	Risk Ratio (95% CI)
Omalizumab	*
Mepolizumab	0.45 (0.11-1.80)
Reslizumab	0.67 (0.37-1.20)
Benralizumab	2.70 (0.86-8.49)
Dupilumab 200 mg	0.50 (0.27-0.92)
Dupilumab 300 mg	2.23 (1.14-4.38)

*The Cochrane review reported qualitatively that there were no differences in drug discontinuation due to adverse events compared with placebo.[14]

The only consistent adverse event that was more common in the drug arm of the randomized trials compared with the placebo arm was injection site reactions. They were about twice as common in the drug arm as in the placebo arm for most the drugs. Reslizumab was the exception, which may be due to the IV administration of the drug. However, the confidence interval for reslizumab was wide (Table 3.10).

Table 3.10. Risk Ratio for Injection Site Reactions

Treatment	Risk Ratio (95% CI)
Omalizumab	1.72 (1.33-2.24)
Mepolizumab	1.98 (1.06-3.72)
Reslizumab	0.62 (0.20-1.89)
Benralizumab	1.43 (0.81-2.52)
Dupilumab 200 mg	2.80 (1.70-4.61)
Dupilumab 300 mg	1.79 (1.24-4.38)

Other Harms

Both omalizumab and reslizumab carry a black box warning for anaphylaxis, which can occur with the first dose or shortly after doses given more than a year on therapy. Patients must be taught the signs and symptoms of anaphylaxis and clinicians need to be prepared to manage anaphylaxis. The estimated rate of anaphylaxis for omalizumab is 0.1%.[8] The estimated rate of anaphylaxis for reslizumab is 0.3%.[9]

The most common side effects of omalizumab are myalgias, fatigue and injection site reactions. During the five-year follow-up of omalizumab mandated by the FDA, there was a suggestion of an excess of transient ischemic attacks, myocardial infarctions, and pulmonary hypertension, but this was not confirmed in a review of 25 randomized, placebo controlled clinical trials.

The most common side effects of mepolizumab are headache, fatigue, nasopharyngitis and injection site reactions. Hypersensitivity reactions have been reported after receiving mepolizumab. There may also be a small risk of herpes zoster. However, in the initial clinical trials, only three subjects receiving mepolizumab developed herpes zoster compared to two subjects who received placebo, which may be a chance finding.

The most common side effect of reslizumab is oropharyngeal pain.

The most common side effects with benralizumab are headache, pharyngitis and pyrexia. Hypersensitivity reactions have been reported rarely with benralizumab. Benralizumab binds to the Fc receptor on natural killer cells which markedly lowers eosinophils by inducing apoptosis. It is unclear if this has any important clinical implications at this time.

In the trials of dupilumab for atopic dermatitis, injection site reaction, nasopharyngitis, and headache were the most common side effects and there appeared to be increased rates of conjunctivitis. In the trials for asthma, only injection site reactions were more common in the dupilumab group (9% vs. 4%). Among the other common AEs in the asthma trials, the risk was lower or similar with dupilumab compared with placebo (viral upper respiratory infections 9% vs. 18%; bronchitis 7% vs. 6%; sinusitis 7% vs. 4%; and influenza 3% vs. 6%)

Subgroup Analyses

Pediatric Patients

The pivotal trials for several of the drugs enrolled patients with ages younger than 18 years, but the number of participants were small. Two randomized trials of omalizumab specifically enrolled pediatric patients.[67,68] The first randomized 334 children ages 6-12 to omalizumab or placebo. Follow-up was 24 weeks, but only 16 weeks at stable dose ICS followed by eight weeks of ICS dose reduction. Patients on omalizumab had fewer exacerbations (18.2% vs. 38.5%, p<0.001) during the dose reduction phase and more patients on omalizumab were able to completely stop ICS (55% vs. 39%, p=0.004).[68] It is noteworthy that 39% of patients in the placebo group were able to stop ICS use, which suggests overtreatment in a substantial proportion of pediatric patients. It may be reasonable to attempt steroid down-titration prior to initiating biologic therapy.

The second trial randomized 419 children ages six to twenty years (mean 11 years) to omalizumab or placebo and followed them for 60 weeks.[67] Patients on omalizumab had fewer exacerbations (30.3% vs. 48.8%, p<0.001), fewer days with asthma symptoms (1.48 vs. 1.96 days per two weeks, p<0.001), and fewer days missed from school (0.16 vs. 0.25 per 2 weeks, p=0.038). Similarly, there were fewer hospitalizations for asthma among the participants randomized to omalizumab (1.5% vs. 6.3%, p=0.02). These benefits were seen despite greater reductions in the dose of inhaled corticosteroids (p<0.001) and LABA (p=0.003) for patients in the omalizumab group.

Omalizumab is the only biologic with studies dedicated to the pediatric population. The two studies consistently demonstrated a reduction in asthma exacerbations with fewer hospitalization and days missed from school in the larger, longer study. The studies demonstrated these benefits while also demonstrating a reduction in the need for ICS and LABA therapies.

Patients on Oral Corticosteroids

There are published studies for omalizumab,[69] mepolizumab,[70] benralizumab,[71] and dupilumab[17] that specifically evaluated the reduction in OCS use in patients requiring chronic OCS for asthma. We did not identify any studies of reslizumab for patients on chronic OCS.

A subgroup of 82 patients in the open label EXALT study were using OCS at baseline.[69] By week 32, patients randomized to omalizumab had greater reductions in their dose of OCS (-45% vs. +18.3%, p=0.002) and there was a trend towards a greater proportion who were able to completely stop OCS use (32.2% vs. 13%, p=0.08).

The SIRIUS study randomized 135 patients with severe eosinophil asthma on OCS to either mepolizumab or placebo.[70] The median reduction in OCS dose was 50% in the mepolizumab group versus 0% in the placebo group (p=0.007). A greater proportion of patients in the mepolizumab group were able to reduce OCS to ≤ 5 mg per day of prednisone (54% vs. 32%, p=0.02), though the

proportions able to stop OCS were not different (14% vs. 8%, p=0.41). Despite the greater reduction in OCS, patients in the mepolizumab group had lower rates of exacerbations (1.44 vs. 2.12, p=0.04) and a greater reduction in symptoms on the ACQ (difference=0.52, p=0.004).

The ZONDA study randomized 220 patients with severe eosinophilic asthma on OCS to either benralizumab 30 mg every four or eight weeks or to placebo every four weeks.[71] The median reduction in OCS dose was 75% in the two benralizumab groups versus 25% in the placebo group (p<0.001). More patients receiving benralizumab were able to stop OCS use (56% every 4 weeks; 52% every eight weeks; 19% placebo, p<0.001 and p=0.002 respectively). The final dose was ≤ 5 mg per day prednisone for 61% of patients in the four-week benralizumab group, 59% in the eight-week group compared with 33% in the placebo group (p<0.001 and p=0.002 respectively). Even with greater reductions in OCS use, the benralizumab groups had lower rates of asthma exacerbations (rate ratio 0.30, 95% CI 0.17-0.53, p<0.001 for the eight-week group).

The LIBERTY ASTHMA VENTURE study randomized 210 patients with severe asthma on OCS to dupilumab 300 mg SC every two weeks for 24 weeks.[17] The mean reduction in OCS dose was 70% in the benralizumab group versus 42% in the placebo group (p<0.001) and the median reduction was 100% versus 50% (p<0.001). More patients receiving dupilumab were able to stop OCS use (52% vs. 29%, p=0.002). The final dose was <5 mg per day prednisone for 72% of patients in the dupilumab group compared with 37% in the placebo group (p<0.001). Even with greater reductions in OCS use, the benralizumab groups had significantly lower rates of asthma exacerbations (0.65 vs. 1.60, p<0.05).

Across the studies of these four drugs (omalizumab, mepolizumab, benralizumab, and dupilumab), the initial daily dose of OCS was between 10 and 15 mg of prednisone. Despite heterogeneity in the patient populations and study designs, the benefits were similar across the trials: between 20% and 30% more patients compared with placebo were able to reduce their dose of prednisone to <5 mg per day or to completely stop their prednisone. It is unknown if patients treated with reslizumab would achieve similar reductions in OCS. As with ICS in the pediatric population, a remarkable proportion of patients in the placebo group of these studies were able to stop OCS use (8%, 13%, 19%, and 29% of patients in the four studies). A trial of OCS dose down-titration may be useful prior to starting biologic therapy.

Patients with Blood Eosinophils ≥ 300 cells/µL, ≥ 2 Exacerbations in the Prior Year, and ACQ ≥ 1.5

Four of the five biologic drugs considered in this review are indicated for eosinophilic asthma and the fifth drug has published data suggesting that there are greater relative reductions in exacerbation rates for patients with eosinophils ≥ 300 cells/µL compared with patients with lower eosinophil counts (see Table 3.11 below).[16,19] Because the benefits seemed greater in this population and because it may represent a more homogenous population, we performed a network meta-analysis (NMA) in this subgroup. In addition, to further limit the analysis to patients with

similar characteristics, we requested data from manufacturers in the subgroup of patients with eosinophils ≥ 300 cells/µL, two or more exacerbations in the year prior to randomization, and an ACQ ≥ 1.5. We received data in confidence from three manufacturers to support this analysis and data were available for the remaining drugs in a similar subgroup. Data informing the analysis as well as details about our methods are reported in Appendix D.

Table 3.11. Rate Ratio for Asthma Exacerbations by Eosinophil Level

Treatment	Eos < 300 (95% CI)	Eos ≥ 300 (95% CI)
Omalizumab	1.07 (0.45-2.53)	0.41 (0.20 -0.80)

Eos: blood eosinophils (cells/µL)

The network diagram (Figure 3.1) shows that all of the biologics connect through the placebo group, but there are no head to head trials (other than the two doses of dupilumab) to assess whether our indirect estimates are consistent with direct estimates.

Figure 3.1. Network Diagram for NMA of Asthma Biologic Therapies in Patients with Eosinophil Counts ≥ 300 cells/µL, ≥ 2 exacerbations in the prior year, and ACQ ≥ 1.5

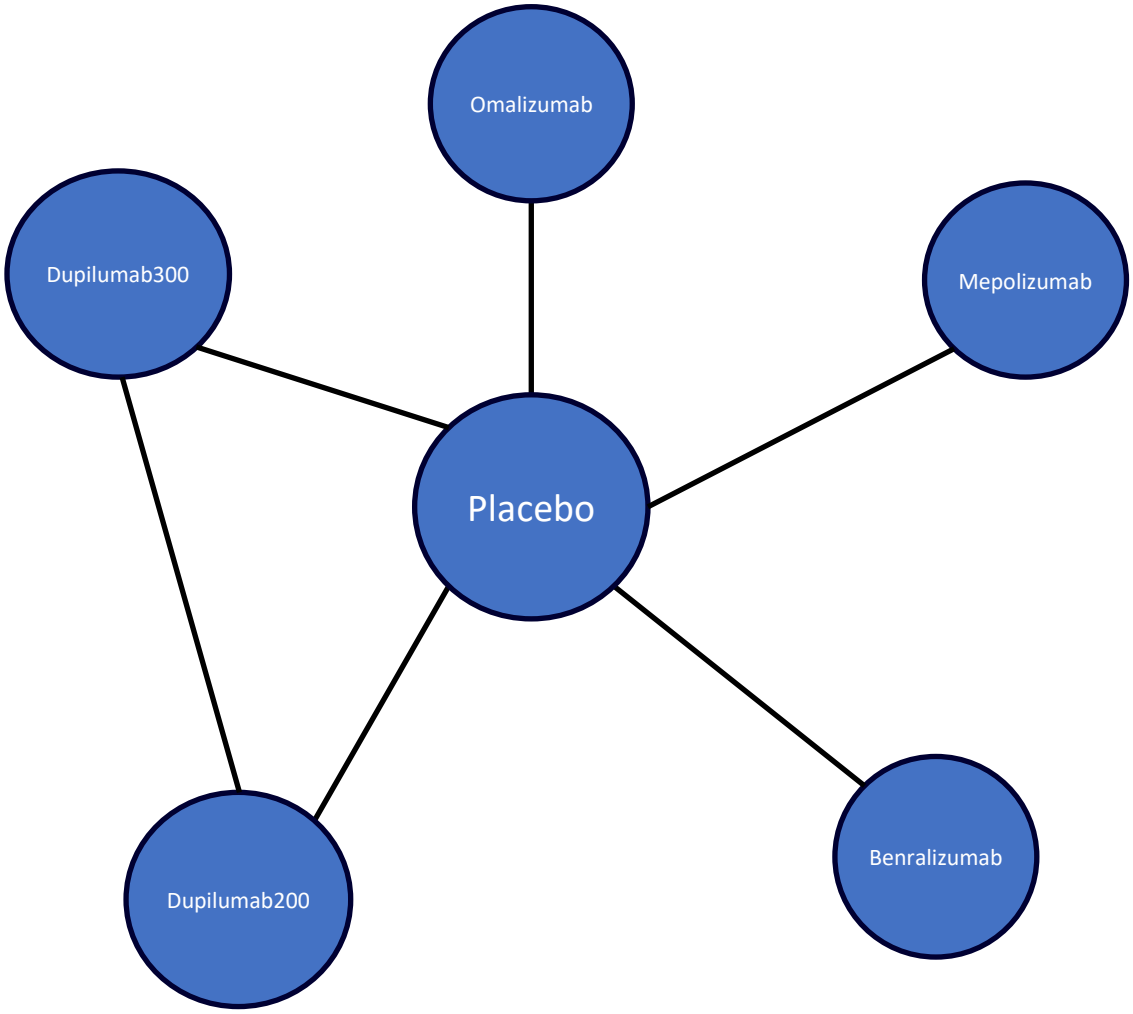


Table 3.12 below shows the pairwise comparisons for all of the drugs as well as placebo.

Table 3.12. NMA Results Comparing the Relative Rate of Asthma Exacerbations for Five Biologic Therapies

Dupilumab200						
1.00 (0.33, 3.00)	**Dupilumab300**					
0.78 (0.15, 4.09)	0.78 (0.15, 4.20)	**Omalizumab**				
0.75 (0.16, 3.70)	0.75 (0.16, 3.69)	0.97 (0.18, 5.20)	**Reslizumab**			
0.72 (0.18, 2.89)	0.72 (0.18, 2.87)	0.92 (0.21, 4.10)	0.95 (0.24, 3.86)	**Mepolizumab**		
0.44 (0.11, 1.74)	0.44 (0.11, 1.76)	0.57 (0.13, 2.41)	0.59 (0.15, 2.30)	0.62 (0.20, 1.89)	**Benralizumab**	
0.26 (0.08, 0.79)	**0.26 (0.08, 0.80)**	0.33 (0.10, 1.14)	0.34 (0.11, 1.03)	**0.36 (0.16, 0.81)**	0.59 (0.26, 1.29)	**Placebo**

Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

In Table 3.12, only dupilumab (both doses) and mepolizumab were significantly better than placebo due to relatively small numbers of patients in this subgroup for omalizumab, mepolizumab and benralizumab. The point estimates for omalizumab, reslizumab, and mepolizumab were nearly identical. Dupilumab had the largest reduction in exacerbations and benralizumab the smallest, but none of the comparisons between drugs were statistically significant. The estimates for the RR for dupilumab, omalizumab, reslizumab, and mepolizumab are markedly better than those reported in the full trial, but the NMA estimate for benralizumab is nearly identical to its primary estimate, because it was studied in patients with severe asthma, an ACQ≥1.5, at least 2 exacerbations in the prior year, and a baseline eosinophil count ≥ 300 cells/µL. These results are more robust than those presented in the draft report because of additional data provided by manufacturers. They demonstrate that the relative and absolute benefits of all of the drugs are greatest in patients with high eosinophil counts (≥ 300 cells/µL) and more exacerbations in the prior year (≥2).

Controversies and Uncertainties

There are several important uncertainties. First, there is a lack of evidence on the long-term safety and effectiveness of these drugs, particularly in older patients, given that many of the patients taking the drugs are relatively young when they start and have 30 to 70-year life expectancies. The potential cardiovascular harms identified in the 5-year follow-up of omalizumab highlight the importance of carefully evaluating these therapies over the long-term. The length of follow-up in some of the randomized trials was only 24 weeks and no trial was longer than 15 months. The long-term extension trials and real-world experience with omalizumab and mepolizumab are reassuring, but uncontrolled.

There is no clear definition for a response to therapy to help guide patients and clinicians in deciding when to stop one therapy and consider switching to another. Similarly, apart from the allergic phenotype and eosinophilia, there are currently no biomarkers to help clinicians decide

which of these drugs may be most appropriate for the individual patient confronting the decision to start one of these drugs.

A related question is defining the optimal length for biologic therapy. Studies of omalizumab and mepolizumab report worsening asthma when treatment is stopped. To date, it does not appear that biologic therapy results in long-term remission of asthma. However, some experts expressed hope that these therapies could impact long-term remodeling of the airways, which could lead to greater benefits than were observed in the clinical trials.

While quality of life is an essential driver of the overall evaluation of the effectiveness of these therapies, there is no standard assessment of quality of life used across all studies. Ideally, there would be one measure, assessed at a standard time point, that could be used to compare quality of life across interventions.

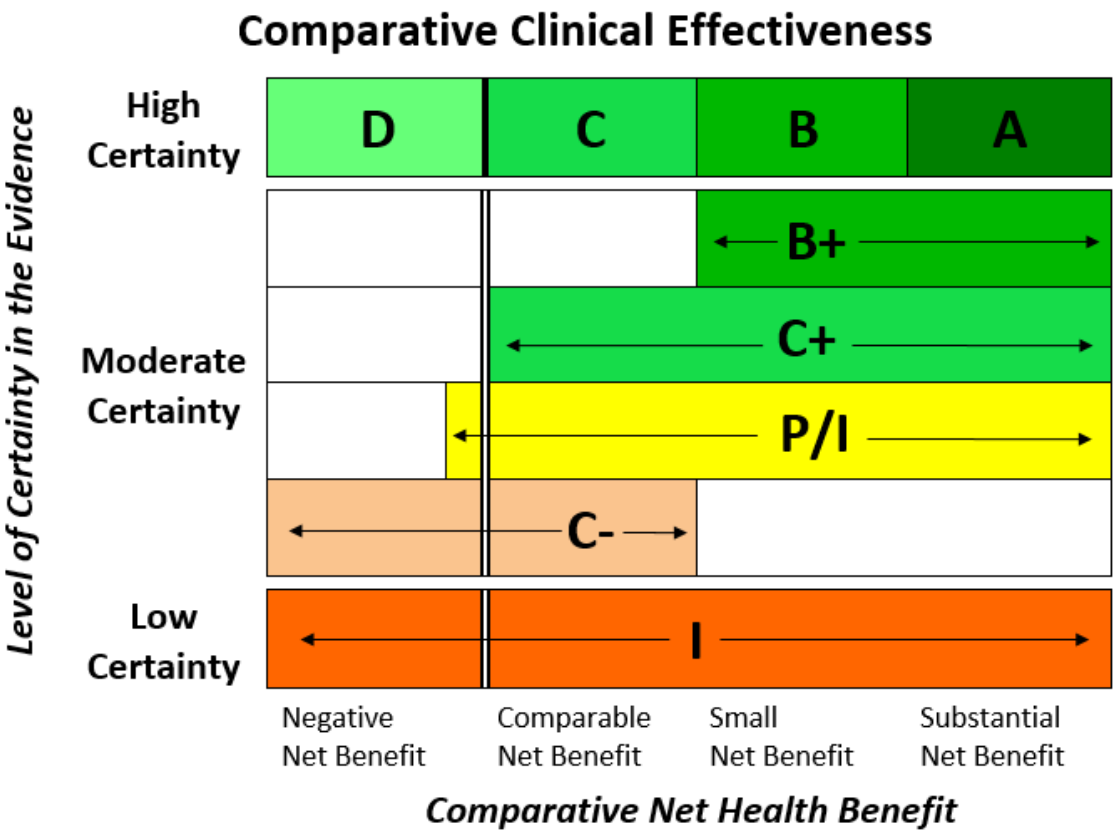
Eosinophils are part of the immune response to parasitic infections. It is unknown if the therapies that decrease eosinophil counts will affect patients' ability to fight such infections. Current guidelines recommend that physicians treat patients for existing parasitic infections prior to initiating anti IL-5 therapy.

Finally, the current evidence base precludes reliable comparative effectiveness analyses between the five drugs as highlighted by Drs. Drazen and Harrington in their editorial accompanying the publication of the pivotal trials of dupilumab.[26] They assert that they regard the treatments targeting type 2 inflammation "as essentially equivalently effective treatments." They call for researchers to design and implement a large, pragmatic trial comparing all of the available drugs in order to clarify whether or not there are clinically important differences between the drugs and to facilitate studies of biomarkers that could identify subgroups of patients likely to benefit from one of the specific drugs.[26]

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.2), we assigned evidence ratings to each of the biologics relative to standard of care (Table 3.13). As noted previously, the lack of head-to-head data as well as our inability to indirectly compare the regimens through network meta-analysis precluded assessment of the comparative net health benefit of these regimens relative to each other.

Figure 3.2. 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 or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Omalizumab

For patients ages 12 years and older with moderate to severe persistent asthma who have a positive skin or blood test to year-round airborne allergens and whose symptoms are not well-controlled by inhaled corticosteroids, we judge there to be high certainty of a small net benefit for omalizumab 75 to 375 mg SC every two to four weeks as add-on maintenance treatment compared with standard of care including high dose ICS plus LABA or additional controller medications. Omalizumab carries a black box warning for anaphylaxis and requires administration by a health care professional. In addition to trials in adults, there are randomized trials supporting comparable

benefits in the pediatric population, trial extension studies confirming ongoing benefits from therapy up to nine years, and real-world observational studies reporting similar benefits to those observed in the randomized trials. There remains some uncertainty about the long-term durability of the benefits of the therapy when used for many years and about the potential harms from modulation of the immune system, but these have decreased with the additional data. In addition, there are suggestions of cardiovascular adverse events that may be more important in patients older than those studies in the randomized trials. The benefits in terms of the reductions in exacerbations and improvement in quality of life are modest, rather than substantial and the harms are small. Therefore, we judge the current body of evidence on omalizumab to be "incremental" compared with standard of care ("B").

Mepolizumab

For patients ages six years and older with severe eosinophilic asthma, we judge there to be high certainty of a small net benefit for mepolizumab 100 mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS plus LABA or additional controller medications. Mepolizumab requires administration by a health care professional. Since the prior ICER review of mepolizumab (C+ rating, comparable or better), there are trial extension studies confirming ongoing benefits from therapy beyond one year of therapy and some real-world observational data supporting similar benefits to those observed in the randomized trials. In addition to trials in adults, there are randomized trials supporting comparable benefits in the pediatric population, trial extension studies confirming ongoing benefits from therapy up to five years, and real-world observational studies reporting similar benefits to those observed in the randomized trials. There remains some uncertainty about the long-term durability of the benefits of the therapy when used for many years and about the potential harms from modulation of the immune system, but these have decreased with the additional evidence. The benefits in terms of the reductions in exacerbations and improvement in quality of life are modest, rather than substantial and the overall harms are small. Therefore, we judge the current body of evidence on mepolizumab to be "incremental" compared with standard of care ("B").

Reslizumab

For adult patients 18 years and older with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for reslizumab 3 mg/kg IV every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. Reslizumab carries a black box warning for anaphylaxis and requires administration by a health care professional. There is moderate certainty because the randomized trials demonstrating efficacy were relatively small studies of short duration given the lifetime time horizon for potential use of reslizumab. 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. The consistent benefits and minimal harms observed with the

two other asthma biologics targeting the IL-5 pathway, reduces the uncertainty somewhat. Ongoing post-marketing trials and extension studies evaluating reslizumab 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 reslizumab to be "comparable or better" compared with standard of care ("C+").

Benralizumab

For patients ages 12 years and older with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for benralizumab 30 mg SC every four weeks for twelve weeks, then every eight weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. Benralizumab requires administration by a health care professional. There is moderate certainty because the randomized trials demonstrating efficacy were relatively small studies of short duration given the lifetime time horizon for potential use of benralizumab. 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. The consistent benefits and minimal harms observed with the two other asthma biologics targeting the IL-5 pathway, reduces the uncertainty somewhat, but it targets the receptor rather than IL-5 itself and causes greater depletion in eosinophils. Ongoing post-marketing trials and extension studies evaluating benralizumab 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 benralizumab to be "comparable or better" compared with standard of care ("C+").

Dupilumab

For patients ages 12 years and older with moderate to severe asthma with at least one exacerbation in the prior year, we judge there to be moderate certainty of a comparable or better net benefit for dupilumab 200 mg or 300 mg SC every two weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and an additional controller medication. There is moderate certainty because the two trials 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. A unique benefit of dupilumab that matters to patients is that it may be self-administered at home, while the other biologics require administration by a health professional. The common AEs reported in studies of dupilumab for atopic dermatitis were not replicated in the trials for asthma. Ongoing post-marketing trials and extension studies evaluating dupilumab 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 (opportunistic infections, anaphylaxis). Therefore,

we judge the current body of evidence on dupilumab to be "comparable or better" compared with standard of care ("C+").

Comparisons Between Biologic Therapies for Asthma

There are no head to head trials and the heterogeneity in the populations studied in the randomized trials precluded performing a network meta-analysis. When comparing the effect sizes from the meta-analyses of the individual drugs compared with placebo, the improvements in exacerbation rates and quality of life appear qualitatively similar, but this may be misleading. We attempted to perform a network meta-analysis in the population of patients with severe asthma with baseline eosinophil counts ≥ 300 cells/µL, but there remained significant heterogeneity in the populations. In addition, the results did not differ substantially from the estimates from the original trials, which was unexpected as analyses for several of the trials found substantially greater relative risk reductions for exacerbations in the subgroup of patients with high baseline eosinophil counts. Therefore, there is low certainty in the comparative clinical effectiveness of the agents: an I rating or insufficient.

Table 3.13. ICER Ratings for Biologic Therapies for the Treatment of Asthma

Treatment	ICER Evidence Rating
Omalizumab	B: Incremental
Mepolizumab	B: Incremental
Reslizumab	C+: Comparable or better
Benralizumab	C+: Comparable or better
Dupilumab 200 mg	C+: Comparable or better
Dupilumab 300 mg	C+: Comparable or better
Between drugs	I: Insufficient

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of five biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the treatment of moderate to severe uncontrolled asthma with evidence of type 2 inflammation in adults and in children six years and older. This analysis represents an update of our prior analysis on this topic.[27] The population for this updated review was designated with a broad intention to capture the existing or expected FDA indications for all the relevant biologics, though not all of the therapies are indicated for use in younger children or patients with moderate asthma (refer to Table 3.1 in the clinical section). Quality-adjusted survival and health care costs were estimated for each biologic and its relevant comparators using the health care sector perspective. Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated comparing each intervention to its comparator. The model was developed in Microsoft Excel 2016 (Redmond, WA) and followed the general structure of the Institute for Clinical and Economic Review (ICER) 2016 mepolizumab review with updates to accommodate best-available evidence and the additional agents.[27] The model framework and assumptions are described in detail below.

4.2 Methods

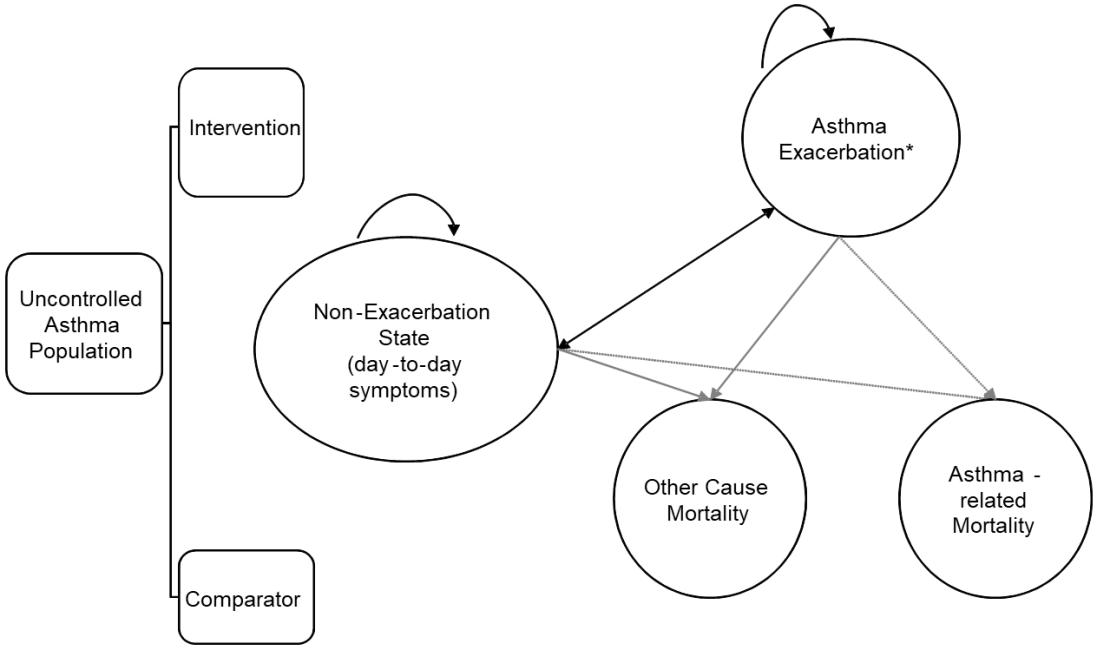
Model Structure

The decision analytic model structure was informed by the primary aim, previous modeling evidence, the evidence review, and stakeholder input. The model structure was based on formerly developed models assessing the cost-effectiveness of asthma biologics including mepolizumab and omalizumab.[72,73]

The Markov model included three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst without emergency department (ED) or inpatient care, asthma-related ED visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality) (Figure 4.1). The model structure was similar to other published asthma cost-effectiveness analysis (CEA) models, including ICER's 2016 report on mepolizumab and related peer-reviewed manuscript[27,73] and the omalizumab model for patients with severe uncontrolled asthma described in the National Institute for Health and Care Excellence (NICE) appraisal determination in 2013 and elsewhere.[72,74-78] Compared to ICER's 2016 initial report on mepolizumab, this updated model structure allowed for one evaluation of treatment responders (where patients who respond to therapy remain on that therapy, and

those who do not have the therapy discontinued) and a separate set of inputs for those who were defined as treatment responders. Treatment responders versus non-responders and their corresponding treatment duration were modeled as a scenario analysis due to heterogeneous and limited responder evidence across the biologic agents.

Figure 4.1. Model Framework



*Exacerbations are defined as three mutually exclusive and exhaustive subcategories:

1. Asthma related event that requires an oral steroid burst (but not emergency department or hospitalization)
2. Asthma related event that requires admittance to the emergency department (but not a hospitalization)
3. Asthma related event that requires a hospitalization

A lifetime horizon was assumed in the base-case, consistent with the ICER Value Framework and other asthma cost-effectiveness models.[74,79,80] The discount rate for all future costs and outcomes was 3% per year.

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 published cost-effectiveness analyses[72,76] and asthma guidelines that suggest new exacerbation events should only be considered after at least a 7-day period from a prior event.[81]

Key clinical inputs for the model, informed by the evidence review, included exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, asthma control, biologic treatment response, and adverse events.

Model outcomes for each intervention included total drug and non-drug health care costs, life years (LY) gained, quality-adjusted life years (QALYs) gained, and annualized asthma exacerbations.

Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. First, a modified societal perspective was completed to account for costs of lost productivity and work due to asthma. Second, a scenario that evaluated the possible costs and outcomes associated with long-term biologic treatment only for treatment responders was modeled with noted evidence gaps. In this scenario, biologic non-responders were assumed to revert to standard of care after failing to respond to the biologic treatment; non-responders were assigned standard of care average costs and outcomes. Finally, we completed a scenario analysis based on the ≥ 300 eosinophil count population stratification, using trial results across biologics in patients with elevated eosinophil counts.

Target Population

Adults and children ages six years and older with moderate to severe, uncontrolled asthma and evidence of type 2 inflammation characterized the population of focus for this updated review. The population was designed to be intentionally broad to capture the indicated populations for all identified biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma.

Table 4.1 presents the base-case model cohort characteristics for the five interventions of interest in this review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab). Best-available evidence for Table 4.1 was derived from the clinical review averaged across the included clinical review studies and biologics. Plausible ranges including a lower and upper value for listed characteristics were tested in one-way sensitivity and scenario analyses. Only characteristics that were used within the economic model are displayed in Table 4.1. See the clinical review for further description of patient cohort characteristics.

Table 4.1. Base-Case Model Cohort Characteristics

Characteristic	Across All Biologic Agents*
Mean (SD) age in years	46 (42-50)
Mean (SD) weight (kg)	85 (75-95)[82]
Percent female	62% (60%-64%)
Percent Chronic OCS Users†	17% (13%-28%)

*Values displayed are derived from the clinical review unless otherwise specified, averaged over trials; plausible ranges include the minimum and maximum values from an individual trial evidence, where available.
†Chronic oral steroid (OCS) definitions differ by evidence source but can be interpreted as the proportion of the biologic eligible cohort that use > 5 mg per day of prednisone or equivalent with high levels of adherence.

Treatments

Interventions

The list of included interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. Each intervention of interest, represented in the list of asthma biologics below, was added on to a standard of care (SoC) comparator.

- Omalizumab 75-375 mg by subcutaneous injection once every two or four weeks
- Mepolizumab 100 mg by subcutaneous injection once every four weeks
- Reslizumab 3 mg/kg by intravenous infusion once every four weeks
- Benralizumab 30 mg by subcutaneous injection once every four weeks for three doses; then every eight weeks
- Dupilumab 200mg or 300 mg by subcutaneous injection once every two weeks

Dupilumab dosing for asthma includes the 200mg and 300mg strength per the Food and Drug Administration. Given that both doses have the same price per administration and comparable efficacy and safety signals, the long-term cost-effectiveness section of the report considered the doses to be interchangeable.

Comparators

The comparators of interest were SoC, typically defined as daily inhaled corticosteroids plus at least one additional controller therapy.

Key Model Characteristics and Assumptions

The base-case analysis took a health care sector perspective, focusing on direct medical care and drug costs. Cycle length is two weeks. Costs and outcomes were discounted at 3% per year. Model assumptions are described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Base-case utility for the non-exacerbation health state was different for biologic plus SoC vs. SoC alone due to potential improvements in day-to-day symptoms.	Without direct elicitation of utilities in trials comparing biologic plus SoC vs. SoC alone, we relied on evidence of patient reported outcome (PRO) instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the Saint George's Respiratory Questionnaire mapping algorithm.[83] A manufacturer submission to NICE used a similar approach.[28] Although other utility relationships are known for the Asthma Quality of Life Questionnaire,[84] using such a mapping produced less favorable results for all biologics.
Long-term biologic treatment only for treatment responders was included as a scenario analysis for all biologics.	The ability to evaluate treatment responders within this updated review was consistent with recent asthma biologic health technology assessments.[28] However, given heterogeneity across treatment responder definitions, stakeholder comments, limited comparative outcomes evidence tied to treatment responders vs. non-responders, and limited understanding of how such responder definitions would be implemented in US practice settings, the inclusion of the potential impact of treatment responders was reserved as a scenario analysis.
Exacerbations requiring only an oral steroid burst were assumed to not impact mortality over and above the severe asthma-related mortality rate for all living health states in the model.	Increased mortality rates were included for exacerbations requiring emergency care (hospitalizations or ED visits), consistent with United Kingdom evidence. No added mortality was included for oral steroid burst exacerbations given that the risk of death found in the United Kingdom evidence was similar to the annual US risk of severe asthma-related mortality conditioned on age, a parameter that was already incorporated into the model.[28,29]
Reduction in daily chronic oral glucocorticoid dose to a level of 5 mg or less was not harmful in terms of adverse events or disutility.	5 mg per day was a typical literature cutoff, with chronic doses above 5 mg considered harmful and associated with both costs and disutilities.[85]
Disutility values for hospitalizations, ED visits, and oral steroid bursts were assumed to be for two weeks.	Disutility was comparable to the NICE omalizumab and mepolizumab reference-case.[28,74]
In order to eliminate differences across baseline characteristics, such as age, that may impact lifetime costs and outcomes, we averaged over baseline characteristics to estimate the same model cohort's baseline age, gender, weight, proportion of chronic oral steroid users, and SoC annualized exacerbation rates.	The comparative clinical evidence was allowed to be unique for each biologic plus SoC vs. SoC alone; differences in SoC cohort characteristics across evidence sources were normed as we did not expect such characteristics to have a significant effect on the incremental lifetime findings. The normed plausible characteristic ranges were tested using sensitivity and scenario analyses.

ED: emergency department, SoC: standard of care

Model Inputs

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The inputs that informed the model are described below.

Clinical Inputs

Treatment Regimen

Table 4.3 indicates the inputs corresponding to the regimen for the specified interventions. Further, Table 4.3 includes the findings for each regimen as compared to SoC alone on the proportion of patients who are on oral corticosteroids at the end of study, generally from oral steroid sparing studies. Consistent with NICE reports, we assumed 100% compliance and adherence for those who respond to biologic add-on therapy.[28,74]

Table 4.3. Treatment Regimen

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Treatment Dose	75-375 mg every 2 to 4 weeks (assumed 36 vials per year with wastage)[72]	100 mg every 4 weeks	3.0 mg/kg every 4 weeks (assumed 2 to 3 single-use 100mg/ml vials per administration or 36 per year with wastage)	30 mg every 4 weeks (first 3 doses) then every 8 weeks[62]	200mg or 300 mg every 2 weeks[16]
Route of Administration	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Relative Reduction in Chronic Oral Corticosteroid Use Post Trial (% biologic vs. % SoC with chronic use > 5mg per day)	0.78 (67.8% vs. 87.0%)[69]	0.68 (46% vs. 68%)[70]	1.0 (No comparative evidence reported)*	0.61 (41% vs. 67%)[71]	0.46 (31% vs. 67%)[17]

*For evidence "Not reported," no difference was assumed (i.e., relative reduction of 1.0) between biologic plus SoC vs. SoC alone.

Exacerbation-Related Inputs

Inputs related to exacerbations are detailed in Tables 4.4 and 4.5, consistent with the clinical review.

Table 4.4. Exacerbation-Related Inputs: Rate Ratios for Intervention versus SoC

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab†
Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	0.52 (0.37-0.73)[14]	0.45 (0.36- 0.55)[15]	0.43 (0.33-0.55)[15]	0.59 (0.51- 0.68)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]
Rate Ratio for Exacerbations Resulting in ED visit (without hospitalization)	0.40 (0.19- 0.82)[86]*	0.36 (0.20- 0.66)[15]	0.67 (0.39- 1.17)[15]	0.68 (0.47- 0.98)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]
Rate Ratio for Exacerbations Resulting in Hospitalization	0.16 (0.06- 0.42)[14]	0.31 (0.13- 0.73)[15]	0.67 (0.39- 1.17)[15]	0.68 (0.47- 0.98)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]

*Evidence source was not reported within the clinical review but was included in a prior meta-analysis
†Rate ratio for dupilumab for each subcategory of exacerbation was assumed the same as the overall exacerbation rate ratio that most closely reflected the Food and Drug Administration labeled population.

Table 4.5. Exacerbation Related Inputs: SoC

Characteristic	Standard of Care Across All Biologics
Annualized Exacerbation Rate Per Person Year, End of Study (95% CI)*	1.30 PPY (plausible range: 0.9- 2.3)
Proportion of Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)†	90%[86-88]
Proportion of Exacerbations Resulting in ED visit (without hospitalization) †	5%[86-88]
Proportion of Exacerbations Resulting in Hospitalization**	5%[86-88]

PPY: per person year
*Values displayed are derived from the clinical review unless otherwise specified, averaged over trials; plausible ranges include the minimum and maximum values from an individual trial evidence, where available.
†Assumed based off of values from Ortega et al. 2014, Bousquet et al. 2005, and Castro et al. 2015.

Adverse Events

The evidence suggested no differences in costs or disutility values associated with adverse events between biologics plus SoC versus SoC alone. Chronic oral steroid use and its associated long-run costs and disutility was included within this updated review.

Asthma-Related Mortality

Asthma-related mortality and other cause mortality were modeled for all living health states (non-exacerbation and exacerbation).[28-31] Watson and colleagues, who analyzed a United Kingdom database including 250,043 asthma-related hospital admissions to determine the mortality rate following hospitalizations, described a risk of death linked with asthma-related hospitalizations (2.48%).[30] For the asthma-related hospitalization exacerbation subcategory, the relationship of increased death, consistent with Watson et al., was added to the background of severe asthma-related mortality and other cause mortality. Further, the NICE mepolizumab technology appraisal suggested there may be an increased risk of death for other exacerbation-related subcategories.[28] The National Review of Asthma Deaths report was the largest worldwide study on asthma deaths to date and the first United Kingdom-wide investigation into the topic.[31] They used "death by location" to show indications for death at home, on the way to the hospital, and in the hospital. Due to this evidence, the NICE mepolizumab appraisal suggested that the risk of death for those over age 45 years was 1.79% for those who experienced an asthma-related ED visit. We added the 1.79% risk of death for asthma-related ED visits to the background of severe asthma-related mortality and other cause mortality. The NICE mepolizumab appraisal also suggested the risk of death for those over age 45 years was 0.38% for those who experienced an asthma-related oral steroid burst exacerbation. Given the annual risk of death for those with severe asthma from de Vries et al. was 0.4% per year and due to potential differences in death rates in the US,[29] we assumed no increased risk of death over that of severe asthma-related mortality for the oral steroid burst asthma exacerbation sub category (see assumptions Table 4.2).

Utility Inputs

Model Health States

To adjust for potential quality of life differences, utilities were applied for each model health state. Health state utilities were derived from publicly available literature and applied to the disease states. The utilities for the non-exacerbation health state are presented in Table 4.6. The disutility values for other health states or events are displayed in Table 4.7.

The non-exacerbation health state utility value was allowed to be different for the biologic plus SoC treatment arm versus SoC alone. For the non-exacerbation health state, the clinical evidence from Ortega et al.[87] and Chupp et al.[89] reported on the St George's Respiratory Questionnaire (SGRQ) for mepolizumab plus SoC versus SoC alone.[15] We identified a published mapping between mean total SGRQ scores and the EQ-5D. The mean total SGRQ score of 38.9 for SoC[87] and 31.5 for

mepolizumab plus SoC based on the pooled study mean difference[15] 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).[83]

Without known direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we relied on evidence of patient reported outcome instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the SGRQ mapping algorithm.[83] The improvement in utility based on the SGRQ mapping algorithm suggests mepolizumab is associated with 0.062 higher utility in the non-exacerbation health state compared to SoC alone (See Table 4.6).

Utility relationships are published for the Asthma Quality of Life Questionnaire (AQLQ) with the most applicable utility mapping suggesting a one-unit improvement in AQLQ is associated with an improvement of 0.12 in utility.[84] More sophisticated AQLQ mapping algorithms are published but require sub-domain scores or other more granular-level of AQLQ evidence. Based on the clinical review across all five biologics' mean change differences versus SoC for AQLQ, the corresponding mapped improvement in non-exacerbation health state utility would be between 0.028 and 0.042 as compared to SoC. Because AQLQ improvements were in the same range across all biologics, we assumed the higher SGRQ mapped utility for all biologic treatments in terms of the non-exacerbation health state utility. The decision to use the SGRQ-mapped utility for all biologic treatments was strengthened by prior patient-level research suggesting an omalizumab AQLQ-mapped utility improvement of 0.063 compared to SoC.[65,72] If the AQLQ signals from this report were mapped into utilities (instead of assuming the SGRQ-mapped utility applied to all biologics), lower incremental QALYs would be observed across all biologics versus SoC and less favorable cost-effectiveness estimates would have been produced (see scenario results section for the incremental cost-effectiveness ratio finding for the biologic with the most favorable AQLQ improvement according to the clinical review). Given this utility assumption is more uncertain for biologics other than mepolizumab, we doubled the standard error for all non-mepolizumab biologic-treated non-exacerbation health state utilities.

Table 4.6 shows the associated asthma patient-reported outcome responses for each respective biologic, the mean change difference in AQLQ according to the clinical review and the non-exacerbation mean health state utility for biologic plus SoC versus SoC alone.

Table 4.6. Asthma Patient-Reported Outcome Response and Corresponding Non-Exacerbation Utility

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Asthma Patient-Reported Outcome Measure	AQLQ	AQLQ SGRQ	AQLQ	AQLQ	AQLQ
Asthma Patient-Reported Outcome Mean Change Difference vs. SoC (95% CI)	0.26 (0.05-0.47)[14]	AQLQ: 0.35 (0.08-0.62)[90] SGRQ: -7.4 (-9.5 to -5.3)[15]	0.28 (0.17-0.39)[15]	0.23 (0.11-0.35)[15]	0.26 (0.12-0.40)[16]
Non-Exacerbation Mean Health State Utility for biologic plus SoC vs. SoC alone (SE)*	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.010) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)

AQLQ: Asthma Quality of Life Questionnaire, SGRQ: St. George's Respiratory Questionnaire, SE: standard error, SoC: standard of care

*Utility mapping based on mepolizumab plus SoC vs. SoC alone for the St. George's Respiratory Questionnaire; mepolizumab utility values for the non-exacerbation health state were assumed the same for the other biologics plus SoC, but with double the standard error.

Treatment Disutility Values

Disutility values for the exacerbation health states were assumed to be the same across treatment strategies (i.e., the same for biologic plus SoC vs. SoC alone).[91] 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 steroid burst events. We assigned the pre-post decrement in utilities observed in Lloyd et al.[91] for exacerbation-related events. A two-week duration was assumed for all exacerbation health states, consistent with the model cycle. Although an oral steroid burst or ED visit does not typically last two weeks, the stress and anxiety related to these events may remain over a two-week period.

Severe asthma flare-ups are commonly treated through prescribed bursts of oral corticosteroids (OCS), ranging in intensive treatment periods from five days to two weeks. While consistent use of OCS is associated with a greater likelihood of side effects, a time-limited steroid burst is distinct from chronic OCS.[92]

The disutility of chronic OCS for the proportion of patients using >5 mg daily (-0.023)[75] 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. Table 4.7 displays the disutility values present in the model.

Table 4.7. Disutility Values

Characteristic	Disutility	Source
Exacerbation Requiring Steroid Burst*	-0.1	Lloyd et al. 2007[91]
Exacerbation Requiring ED Visit*	-0.15	Lloyd et al. 2007[91] and assumption
Exacerbation Requiring Hospitalization*	-0.20	Lloyd et al. 2007[91]
Chronic Oral Corticosteroid Use†	-0.023	Norman et al. 2013[75]

*Two-week duration, †Lifetime duration

Treatment Responders

In order to build in a one-time evaluation to identify possible treatment responders for the purposes of modeling long-term biologic treatment, evidence needs include the definition of treatment response and its corresponding time post biologic initiation, proportion who respond, and the associated costs and outcomes within the subgroup who respond. The primary clinical outcomes for the subgroup of responders, all compared to SoC alone, include exacerbation rate ratios, changes in chronic oral steroid use, and changes in non-exacerbation health state utilities. Given the lack of publicly available evidence on treatment response definitions, proportions who respond, and the corresponding comparative outcomes for the reviewed biologics, we included a *what if* scenario on the potential impact that treatment responders may have on lifetime incremental costs and QALYs.

Economic Inputs

Treatment Costs and Details

The unit cost for each intervention is reported in Table 4.8. Net price data that were submitted by the five manufacturers were used wherever calculations or reporting involves net price.

Threshold prices were calculated at the three cost-effectiveness thresholds ($50,000, $100,000 and $150,000 per QALY gained).

Treatment-related costs (SoC and asthma biologics) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states).

Table 4.8. Treatment Costs and Details

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Unit	150 mg vial	100 mg	100 mg/ml vial	30 mg	2 x 200mg or 2 x 300mg
Wholesale Acquisition Cost (WAC)	$1,084.66	$2,868.67	$878.80	$4,752.11	$2,931.54
Manufacturer Net Price (% of WAC)	$802.64* (74% of WAC)	$2,272† (79% of WAC)	$804.10‡ (91% of WAC)	$4,265¥ (90% of WAC)	$2,384.62^ (81% of WAC)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns." Benralizumab will have an additional cost of $6,302.30 for the first year of treatment due to the higher frequency of administration for the first three doses.
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone." Dupilumab will have an additional cost of $1,192.31 for the first year of treatment due to the loading dose.

Health Care Utilization Inputs

Health Care Utilization Costs

Table 4.9 details the health care utilization unit costs that will be used in the model. Unit costs for health care utilization were the same across different treatments and populations.

Unit costs for asthma-related hospital stays, emergency department (ED) visits, and exacerbations requiring an OCS burst were estimated using a cohort of 222,817 US patients with asthma from the Clinformatics DataMart Multiplan dataset. Costs were estimated for 30-day periods after an exacerbation and were summarized as mean health care cost per exacerbation and inflated to 2018 US Dollars.[93] All costs were inflated to 2018 levels using the health care component of the personal consumption expenditure index,[94] in accordance with the ICER Reference Case.[95]

There are likely standard of care (SoC) treatment differences within and across biologic therapies. Given that the biologic interventions were indicated as add-on therapies to SoC, the annual cost of SoC in an incremental analysis compared to SoC alone will approximate an incremental difference of $0. We assumed the same annualized cost of SoC from the prior mepolizumab ICER review and consistent with Whittington et al. 2018.[73]

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. Annual US costs associated with an individual using oral corticosteroids chronically above the 5 mg dose level was $7983.[85] This annual estimate compared chronic oral steroid users to asthma patients who did not use oral steroids.

Costs associated with biologic administration are also displayed in Table 4.9. We assumed that four office visits each year would be associated with standard of care. Therefore, administration costs were assigned to the listed therapies in Table 4.9 for each administration in a year above four. Dupilumab was assumed to be self-administered after training, as described within the Food and Drug Administration label.

Table 4.9. Health Care Utilization Cost Inputs

Health Care Unit Costs	Unit Cost (2018 USD)	Source
Exacerbation-Related Steroid Burst (SD)	$1,538 ($2,626)	Suruki et al. 2017[93]
Exacerbation-Related ED Visit (SD)	$2,072 ($2,751)	Suruki et al. 2017[93]
Exacerbation-Related Hospitalization (SD)	$9,053 ($7,257)	Suruki et al. 2017[93]
Annual Cost for SoC (95% interval)	$6,227 ($5079, $7505)	Whittington et al. 2018[73]
Annual Cost of Long-Term Oral Corticosteroid Use with Adverse Events (SD assumed)	$7983 ($7983)	Lefebvre et al. 2017[85]
Intravenous Treatment Administration (1st Hour) for Reslizumab	$144.72 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 96413)[96] Physicians' Fee and Coding Guide, 2018 (HCPCS code 96413)[96]
Office Visit Treatment Administration for Subcutaneous Office-Administered Biologics for Omalizumab, Mepolizumab, and Benralizumab (Dupilumab assumed to be self-administered after loading dose)	$74.16 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 99213)[96]

ED: emergency department, SD: standard deviation, SoC: standard of care, USD: US dollar

Productivity Costs

In order to estimate a modified societal perspective as a scenario analysis, we included lost productivity costs associated with biologic treated populations versus SoC. The Asthma and Allergy Foundation of America notes that the value of additional days lost attributable to asthma is $93 for students and $301 for adults in the work force.[97] For the purposes of calculations in the model due

to limited evidence on the proportion in the work force or otherwise, we used an average hourly wage of $24.68 per hour ($197.44 per day), reported by the Bureau of Labor Statistics, and multiplied this hourly wage by the average number of hours missed from work based on evidence from omalizumab (1.46 hours per week missed) versus SoC (3.09 hours per week missed).[98,99] We assumed this same level of productivity lost applied across all biologic agents.

Table 4.10 details the additional costs included in the modified societal perspective.

Table 4.10: Productivity Costs

Input	Variable	Source*
Average Hourly Wage	$24.68 per hour	Bureau of Labor Statistics, 2018[98]
Hours missed per week (Asthma Biologic)	1.46	Data on file (Genentech)[99]
Hours missed per week (Standard of Care)	3.09	Data on file (Genentech)[99]

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we conducted a threshold analysis by systematically altering the price of the acquisition cost for each treatment option to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds between $50,000 and $150,000 per QALY gained. Finally, for the three main biologic treatment benefits: non-exacerbation utility improvement, exacerbation reductions, and chronic oral steroid reductions, we computed the incremental cost-effectiveness ratio for one biologic treatment for only assigning a benefit based on non-exacerbation utility improvement, based on only exacerbation reductions, and finally based on only the benefit of chronic oral steroid reductions to demonstrate the impact that each benefit has on the base-case finding.

Scenario Analyses

In addition to the modified societal perspective, we also ran three other scenario analyses for the Evidence Report: 1. Subpopulation of patients with baseline eosinophil counts ≥300 cells/µL and at least two exacerbations in the previous year; 2. Treatment responder scenario using evidence primarily from omalizumab studies and; 3. Collective best-case analyses using inputs that favor the lifetime value toward that of biologic therapy.

The modified societal perspective includes productivity-related costs as specified in Table 4.10 and all other base-case inputs.

For the subpopulation of high eosinophil ≥300 cells/µL, the clinical review conducted a network meta-analysis of exacerbation rate ratios and yielded the following rate ratios for overall exacerbations for each biologic versus SoC: 0.33 for omalizumab versus SoC; 0.36 for mepolizumab versus SoC; 0.34 for reslizumab versus SoC; 0.59 for benralizumab versus SoC; and 0.26 for dupilumab 300 mg versus SoC. No evidence was produced related to the rate ratios or proportion of exacerbation sub-types. Therefore, the same proportions were assumed as in the base-case SoC (90% oral steroid burst, 5% ED visit, and 5% hospitalization). The pooled annualized SoC exacerbation rate per person year was estimated as 1.23 in this subpopulation. No other base-case estimates changed for this scenario analysis.

For the treatment responder scenario, we recognize that biologic agents with longer post-approval clinical experience are more likely to have evidence on response and its consequences. A *what if* responder scenario was generated using evidence from omalizumab studies and assumptions consistent with the following: evaluate response after 16 weeks of treatment, assume 60.5% of biologic-treated population respond, assume the rate ratio for exacerbations in responders to be 0.25 for all subcategories of exacerbation, and assume the utility improvement in the non-exacerbation health state compared to SoC can be fully assigned to those who are identified as responders (0.1025 increase in utility for responders vs. SoC and no increase in utility for non-responders vs. SoC).[75]

For the collective best-case analyses, we used inputs across all assessed biologics that would favor the lifetime value toward the biologics (i.e. lower incremental cost-effectiveness finding) in order to produce three incremental cost-effectiveness findings versus SoC alone: 1. used most favorable exacerbation and chronic oral steroid inputs and the lowest annualized price; 2. #1 and assumed a subpopulation of only those on chronic oral corticosteroids as a part of SoC and; 3. #1 and assumed the responder scenario as previously described. The input values that changed for #1 included the following: average age = 45 years old; % female = 60%; % chronic OCS users on SoC = 28%; SoC exacerbation rate = 2.3 per person year; exacerbation relative rate used most favorable from Table 4.4; chronic OCS relative risk = 0.46; and an annualized cost of $27,800. The input values changed for #2 that were not identified in #1 was only to assume that 100% of the modeled cohort were chronic OCS users on SoC. Finally, the input values changed for #3 that were not identified in #1 are those identified in the *what if* responder scenario text.

We added the collective best-case scenarios to the Evidence Report due to public feedback from the draft evidence report. The feedback rightly pointed out differences in the asthma study populations across the assessed biologics. Differences in asthma study population characteristics and other features such as responder treatment strategies and the subpopulation of chronic oral steroid users suggested a bounding of the value assessments toward favoring the biologic treatments.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Base-Case Results

Base-case discounted costs and outcomes from the model are found in Tables 4.11-4.15 for all five biologic agents. The total lifetime discounted QALYs across biologics are in a narrow range from 16.32 for omalizumab to 16.00 for benralizumab. The total lifetime discounted costs were also in a narrow range from $715,000 for benralizumab and $771,000 for reslizumab. The domains included within the health care sector base-case results as well as those included within the modified societal perspective are listed in the impact inventory (Appendix Table E1).

Table 4.11. Base-Case Discounted Costs and Outcomes from Model: Omalizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Omalizumab¶	$715,000	$41,500	$757,000	16.32
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

¶ Price = $802.64* (150 mg vial)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)".

Table 4.12. Base-Case Discounted Costs and Outcomes from Model: Mepolizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Mepolizumab¶	$717,000	$38,400	$756,000	16.22
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.13. Base-Case Discounted Costs and Outcomes from Model: Reslizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Reslizumab¶	$721,000	$50,000	$771,000	16.06
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.14. Base-Case Discounted Costs and Outcomes from Model: Benralizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Benralizumab¶	$669,000	$45,800	$715,000	16.00
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.15. Base-Case Discounted Costs and Outcomes from Model: Dupilumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Dupilumab¶	$732,000	$31,900	$764,000	16.21
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Base-Case Incremental Results

Base-case discounted incremental results are found in Table 4.16 with all biologics falling in the $300,000 to $400,000 per QALY range. The comparison of base-case discounted incremental results alongside the corresponding biologic treatment's annual price are found in Table 4.17.

Table 4.16. Base-Case Discounted Incremental Results

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$325,000 / QALY	$344,000 / QALY	$391,000 / QALY	$371,000 / QALY	$351,000 / QALY

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.17. Base-Case Incremental Cost-Effectiveness Ratio and Annual Price (side-by-side)

	Base-Case Incremental Cost-Effectiveness Ratio	Annual Price*
Omalizumab	$325,000	$28,900
Mepolizumab	$344,000	$29,500
Reslizumab	$391,000	$28,900
Benralizumab	$371,000	$27,800
Dupilumab	$351,000	$31,000

*Annual price excluding loading dose in year 1 of treatment, and excluding administration costs

Lifetime Annualized Clinical Outcomes

Appendix Tables E2- E6 indicate the average annual lifetime clinical outcomes for all five biologic agents. This analysis investigated the average events per person year for exacerbations resulting in oral corticosteroid burst, ED visit, hospitalization, and death (all cause). The exacerbation rate ratios drive these incremental findings.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty for mepolizumab versus SoC included utility estimates for the biologic and SoC non-exacerbation health state, annual exacerbation rates for SoC, and cost of chronic oral steroid use (Figure 4.2 and Table 4.18). Other biologics had similar findings in terms of importance of inputs and relative impact on findings (See Appendix Figures E1- E4).

No biologic achieved a greater than zero likelihood of meeting the $150,000/QALY or lower threshold (Table 4.19).

Similar to the intent of one-way sensitivity analyses, we conducted additional analyses that isolated each of the three main measures of biologic treatment benefit in order to understand how each benefit component alone impacted the discounted incremental lifetime results. We computed the discounted incremental results for mepolizumab treatment by only assigning a benefit based on non-exacerbation utility improvement (nulling out the exacerbation reduction benefit and chronic oral steroid reduction benefit). The discounted incremental result was $514,000/QALY. Nulling out the non-exacerbation utility improvement and the chronic oral steroid reduction benefit, the exacerbation reductions associated with mepolizumab yielded a discounted incremental result of $1,355,000/QALY. Finally, nulling out the non-exacerbation utility improvement and the exacerbation reduction benefit, the chronic oral steroid reductions associated with mepolizumab yielded a discounted incremental result of $23,792,000/QALY. Similar levels of impact were observed across all other biologic treatments.

Figure 4.2. Tornado Diagram(s) for One-Way Sensitivity Analyses of Mepolizumab versus Standard of Care

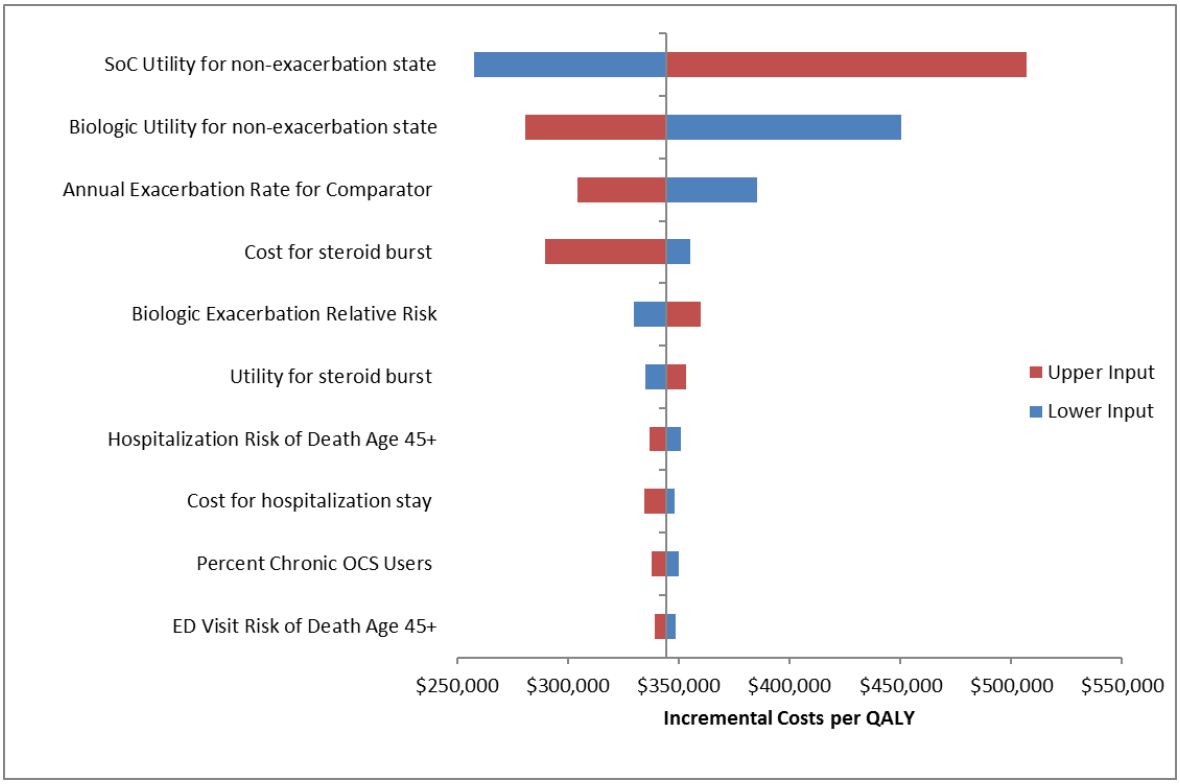


Table 4.18. Tornado Diagram Inputs and Results for Mepolizumab versus Standard of Care

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input*	Upper Input*
SoC Utility for Non-Exacerbation State	$258,000	$507,000	0.74	0.80
Biologic Utility for Non-Exacerbation State	$451,000	$281,000	0.81	0.85
Annual Exacerbation Rate for Comparator	$385,000	$304,000	0.78	1.95
Cost for Exacerbation-Related Steroid Burst	$355,000	$290,000	$0	$9,172
Biologic Overall Exacerbation Relative Risk	$330,000	$360,000	0.34	0.54
Utility for Exacerbation-Related Steroid Burst	$335,000	$353,000	0.57	0.76
Hospitalization Risk of Death Age 45+ Years	$351,000	$337,000	0.021	0.029
Cost for Hospitalization Stay	$348,000	$335,000	$702	$27,798
SoC Percent Chronic OCS Users	$350,000	$338,000	10.9%	24.2%
ED Visit Risk of Death Age 45+	$349,000	$339,000	0.015	0.021

ED: emergency department, SoC: standard of care

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table 4.19. Probabilistic Sensitivity Analysis Results: Biologic versus Standard of Care

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Omalizumab	0%	0%	0%
Mepolizumab	0%	0%	0%
Reslizumab	0%	0%	0%
Benralizumab	0%	0%	0%
Dupilumab	0%	0%	0%

QALY: quality-adjusted life year

Scenario Analyses Results

Results from a modified societal perspective that considers lost work and productivity are presented in Table 4.20. To address concerns about using the SGRQ mapping algorithm to estimate non-exacerbation health state utilities for biologic treated patients, we estimated the incremental cost-effectiveness ratio for the biologic that produced the largest AQLQ improvement according to the clinical review (mepolizumab). If we used the AQLQ mapping algorithm instead of the SGRQ mapping algorithm, the incremental cost-effectiveness ratio for mepolizumab was $448,000/QALY (instead of $344,000/QALY in the base-case). Given the even weaker AQLQ improvements observed for the other biologics, the corresponding incremental cost-effectiveness ratios based on the AQLQ mappings would be even higher than $448,000/QALY. Although the evidence is weak or missing for including aspects of treatment responders within the base-case, we conducted a *what if* scenario including costs and outcomes of treatment responders using a uniform set of inputs and assumptions across all biologics (Table 4.21). Such findings may be interpreted as a best-case scenario related to how these biologics may be used in clinical practice, given the best available comparative evidence. Because several of the drugs had trials with data pertaining to the ≥300 count eosinophil category, we designed and implemented a scenario analysis in this subgroup (Table 4.22). Given that only the exacerbation rates changed within the ≥300 eosinophil count subpopulation and did not change substantially from the base-case inputs, the findings for this scenario are similar to that of the base-case. Finally, the findings for the collective best-case scenarios that use SoC and relative signals that most favor the biologics suggest incremental cost-effectiveness ratios in the $200,000s and upper $100,000s per QALY (Table 4.23). Scenario #1 suggests that when using the most severe of baseline characteristics and largest relative clinical signals and lowest biologic cost, the resulting incremental cost-effectiveness moves from the $300,000s per QALY to $224,000 per QALY. Further, when restricting the treated population to only those who are on chronic oral corticosteroids, the finding becomes $173,000 per QALY. And when adding the responder scenario alongside assuming favorable clinical and cost inputs moves to the incremental lifetime findings to $156,000 per QALY.

Table 4.20. Incremental Results for Modified Societal Perspective versus Standard of Care

	Incremental Costs	Incremental QALYs	Incremental Cost-Effectiveness Ratio per QALY
Omalizumab	$524,000	1.73	$303,000 / QALY
Mepolizumab	$524,000	1.63	$320,000 / QALY
Reslizumab	$538,000	1.48	$364,000 / QALY
Benralizumab	$482,000	1.41	$342,000 / QALY
Dupilumab	$532,000	1.63	$327,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.21. Treatment Responder Scenario Incremental Cost-Effectiveness Ratio

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$ 213,000/ QALY	$ 214,000/ QALY	$222,000 / QALY	$199,000 / QALY	$218,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.22. Eosinophils ≥ 300 Count Incremental Cost-Effectiveness Ratio with ≥ 2 Exacerbations in the Prior Year and Baseline ACQ ≥ 1.5

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$330,000 / QALY	$346,000 / QALY	$346,000 / QALY	$360,000 / QALY	$332,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.23. Collective Best-Case Scenarios

	#1 (favorable base-case inputs)	#2 (#1 and assume 100% chronic OCS users)	#3 (#1 and responder scenario)
Cost per QALY Gained (vs. SoC)	$224,000 / QALY	$173,000 / QALY	$156,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Threshold Analyses Results

Tables 4.24 and 4.25 present the threshold monthly price results for the five biologic agents in the review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) at $50,000, $100,000, and $150,000 per QALY for within-trial and long-run variations.

Table 4.24. Threshold Annual Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Omalizumab	$4,700	$9,000	$13,300
Mepolizumab	$5,100	$9,200	$13,400
Reslizumab	$2,900	$6,500	$10,400
Benralizumab	$4,700	$8,300	$11,900
Dupilumab	$6,000	$10,100	$14,300

QALY: quality-adjusted life year

Table 4.25. Threshold Unit Price Results

Intervention	Unit	WAC per Unit	Manufacturer Net Price	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Omalizumab	150 mg vial	$1,084.66	$802.64*	$130	$250	$370
Mepolizumab	100 mg	$2,868.67	$2,272†	$390	$710	$1,030
Reslizumab	100 mg/ml vial	$878.80	$804.10‡	$80	$180	$290
Benralizumab	30 mg	$4,752.11	$4,265¥	$720	$1,270	$1,820
Dupilumab	2 x 200 or 300 mg	$2,931.54	$2,384.62^	$460	$780	$1,100

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns."
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone."

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

The current ICER model's structure is based on prior asthma model structures including ones developed by Campbell et al., Kim et al., McQueen et al. and the prior ICER report on mepolizumab.[27,72,100,101] The model by Campbell et al. estimated the cost-effectiveness of omalizumab plus SoC versus SoC in patients with moderate to severe persistent asthma. In Campbell et al.'s model, omalizumab treatment had a stopping rule of five years after which patients where shifted to usual care while omalizumab's treatment was over a lifetime in the ICER

model. The rate ratios of OCS burst and asthma exacerbation-related hospitalizations in the ICER model are higher than those used by Campbell et al., while the asthma exacerbation-related ED visits are the same between both models. Difference in non-exacerbation state utilities for biologic treatment versus standard of care treated populations in the ICER model where derived from the SGRQ-EQ-5D mapping algorithm and yielded a biologic-treated improvement of 0.062 in utility while in Campbell et al.'s model utility differences were derived using patient-level data and an AQLQ-EQ-5D mapping algorithm but yielded a comparable utility improvement of 0.063 for omalizumab treated patients versus standard of care alone. The omalizumab price used in both models differ, with omalizumab's net price in the ICER model being approximately 1.4 times the 2008 list price of omalizumab. While exacerbation-related steroid bursts costs and ED costs are substantially higher in the ICER model ($1,538 vs. $120 and $2,072 vs. $548, respectively), exacerbation-related hospitalizations cost are similar between the two models (ICER: $9,053 vs. $9,132). The treatment duration, coupled with higher baseline utilities resulted in higher lifetime discounted QALYs in the ICER model (16.32 vs. 14.19), with the longer treatment duration and higher drug and other costs contributing to higher total costs ($757,000 vs. $174,500) in the omalizumab arm in the ICER model. Comparing incremental results, the ICER model resulted in an incremental cost per QALY of $325,000 while Campbell et al.'s model reported an incremental result of approximately $287,000 per QALY.

A model developed by NICE's Evidence Review Group evaluated the cost-effectiveness of omalizumab as an add-on to SoC versus SoC alone from a UK NHS perspective in patients aged six years and older, with uncontrolled persistent severe asthma.[102] The model structure was similar to what the manufacturer submission was, with health states including day-to-day asthma symptoms (non-exacerbation states), exacerbations states being categorized into clinically significant non-severe (CSNS) and severe (CSS), and asthma and all-cause-related mortality. The CSNS state corresponds to the asthma-exacerbation sub-state requiring only oral-steroid burst without ED visit or hospitalization, while the CSS state corresponds to the ED visit or hospitalization sub-states in the ICER model. Patients subgroups modeling severity categorized by number of hospitalizations, maintenance OCS and number of exacerbations in the NICE model while the ICER model categorized severity by high eosinophil ≥300 cells/µL in a scenario analysis. Baseline exacerbations in the NICE model were derived from the INNOVATE SoC arm for adults and adolescent for both CSNS and CSS, and from IA-05 EUP for children aged 6-11 years. The ICER model uses rate ratios for omalizumab from a Cochrane review (summarized in Comparative Clinical Review Section 3) for the exacerbation-related oral-steroid burst and hospitalization sub-categories. The SoC exacerbation rates were averaged across trials for the five treatments included in the ICER review. Both models apply similar rate ratios of exacerbations for the intervention(s) relative to SoC. The ICER model derived utility estimates for the non-exacerbation health state using mapping algorithms between the SGRQ and EQ-5D while the NICE model used the same findings reported in Campbell et al. However, the NICE model used the utility improvement associated with only omalizumab treatment responders (0.11 vs. SoC) rather than the utility improvement associated with all those who

received omalizumab (0.063 vs. SoC). Exacerbation-related disutility values in both models were derived from the same source, Lloyd et al., which was conducted in the UK.[91] The NICE model used a three-month cycle length while the ICER model uses a two-week cycle length. While the modeled time horizon is 40 years for the NICE model, treatment duration with omalizumab was ten years. The ICER model uses a lifetime time-horizon with treatment duration not being limited to ten years. The ICER model uses a 3% discount rate while the NICE model used a higher 3.5% discount rate. Since the two models cater to different health systems, we do not draw comparisons on treatment-related cost inputs or outcomes. However, comparing QALYs, both intervention and SoC in the ICER model had higher QALYs relative to those in the NICE model in the ≥12-year age group. The higher lifetime discounted QALYs in the ICER model is possibly due to higher ongoing treatment with omalizumab with no stopping rule as seen in the NICE model.

In 2016, ICER conducted a review of mepolizumab plus ICS versus SoC in adults with severe uncontrolled asthma with evidence of eosinophilic inflammation.[27] Model structure for this review followed the same structure as seen in Campbell et al.'s 2010 publication.[72] Compared to the 2016 report on mepolizumab, this updated model structure in the current review allowed for one treatment responder evaluation (where patients who respond to therapy remain on that therapy, and those who do not discontinue therapy) and a separate set of inputs for treatment responders. Comparison of baseline SoC exacerbation rates between the two reviews showed that the 2016 review had a higher rate of 1.74 per year versus 1.3 per year in the current review due to a pooling across biologic therapies in the current review. Proportion of baseline SoC hospitalizations, ED visits and OCS bursts were similar between the two reviews, but mepolizumab-related hospitalization, ED visits and OCS bursts were lower in the current review compared to the 2016 review. Baseline SoC and mepolizumab utilities and exacerbation-related disutility values in both reviews were similar. Like in the 2016 mepolizumab review, the current review did not include an added mortality risk in the exacerbation-related OCS burst subcategory. However additional mortality risk was included for the exacerbation-related hospitalization and ED visit subcategories, with an increased mortality risk for ED visits being applied to the current review. While all treatment related costs in the current review are higher, note that in the 2016 review we used the WAC instead of a net price estimate for mepolizumab, which resulted in higher unit cost of the biologic relative to the current review. Comparing results, the current review versus the 2016 review generated more lifetime discounted QALYs in both the mepolizumab (16.22 vs. 15.12) and SoC (14.59 vs. 13.59) arms, as well as higher costs. The lifetime discounted QALY within treatment increases are driven mainly by the difference in starting age (46 years in current review and 50 years old in 2016 review) but are not thought to significantly impact the incremental findings; higher costs are driven by the higher health care unit costs in the current review. Comparing incremental cost-effectiveness results, the current review resulted in a cost per QALY of approximately $344,000 while the 2016 review resulted in a cost per QALY of approximately $386,000 over a lifetime time horizon, with differences in results driven by differences in mepolizumab treatment cost and other updates such as unit costs and exacerbation rates. The

model by Whittington et al. closely resembles the 2016 ICER review in interventions, target population, methods and results and is hence not described here.[73]

One model submitted to NICE by the manufacturers of mepolizumab compared mepolizumab to SoC in three distinct populations, namely, "modified intention-to-treat (ITT)", a "proposed population" and a "restricted population", and mepolizumab to omalizumab in the "modified ITT" population.[28] The manufacturer "proposed population" comprised patients with blood eosinophil count of ≥150 cells/µL when starting treatment and on systemic corticosteroids. The model used a lifetime horizon and a four-week cycle length, unlike the ICER model's two-week cycle length. Health states in the manufacturer-submitted model included treatment responder evaluation (after one year for mepolizumab and after 12 weeks for omalizumab). If no increase in exacerbation was found at time of assessment, patients could continue on biologic treatment, whereas if an increase in exacerbations was found, patients moved to SoC. The model assumed an attrition of 10% annually, unlike the ICER model which did not assume any treatment-related attrition. The model also assumed a stopping rule of 10-years as time on treatment for biologics, while no such assumption was employed in the ICER model. Treatment effect of mepolizumab was based on the MENSA trial in the manufacturer submitted model. Both models included mortality associated with exacerbation-related hospitalizations, but we found no information on mortality estimates for exacerbation-related ED visits or OCS bursts in the manufacturer submitted model. Utility and disutility estimates in both models are similar. Owing to the difference in setting, we do not compare costs in the two models. We are unable to compare lifetime discounted QALYs between the two models since there no published QALY results, only incremental cost-effectiveness ratios.

4.4 Summary and Comment

The base-case findings from our analysis suggest that the use of asthma biologic agents in the studied populations provides clinical benefit in terms of gains in quality-adjusted survival over that of SoC alone. Due to increased biologic treatment costs, the cost-effectiveness estimates did not meet commonly-cited cost-effectiveness thresholds. This interpretation of the incremental cost-effectiveness findings was robust to one-way and probabilistic sensitivity analyses for all biologic agents. Sensitivity analysis was also used to isolate the impact of the three main biologic agent benefits: non-exacerbation health state utility improvement alone, exacerbation reductions alone (with indirect mortality benefits), and chronic oral steroid reductions alone. The findings from this sensitivity analysis suggested that non-exacerbation health state utility improvements associated with biologic therapy are potentially the most influential benefit input on lifetime discounted cost-effectiveness, followed by exacerbation reductions and finally, the chronic oral steroid reductions. Scenario analyses suggested that the most influential scenarios were including the potential costs and benefits of biologic treatment responders (and non-responders) as well as reserving biologic treatment only in the chronic oral corticosteroid subgroup. In what might be interpreted as an optimistic responder scenario based on best-available comparative evidence, we found incremental cost-effectiveness findings that ranged from $199,000/QALY to $222,000/QALY for the various biologics. The uncertainty in the responder scenario findings is lowest for omalizumab given more available evidence; this uncertainty was not characterized given that the responder scenario is outside of the base-case analysis. When looking at the collective best-case analyses that chose biologically favorable clinical signals and standard of care characteristics, the scenario that included potential costs and outcomes of responders or the scenario that restricted the treatment population to only the chronic oral corticosteroid group resulted in incremental cost-effectiveness findings of $156,000 and $173,000 per QALY, respectively. The modified societal perspective findings reduced the base-case incremental findings by approximately five to ten percent. The ≥ 300 eosinophil subpopulation scenario did not change the results substantially from the base-case.

Limitations

The model analysis was limited by several factors. Long-run clinical evidence on biologic treatment responders as well as discontinuation was not available and, with respect to that limitation, we assumed constant treatment benefits and long-run (lifetime) treatment duration. As the collective best-case treatment responder scenario and chronic oral corticosteroid subpopulation yielded the lowest incremental cost-effectiveness findings, further research is suggested to either refute or support these findings that we cautiously interpret as best case.

Health utility for the day-to-day non-exacerbation health state was identified as the most influential input of biologic benefit with significant uncertainty. Therefore, this is another important area for research.

Mortality was assigned an indirect impact in the model through reduced asthma-related hospitalizations and ED visits. Differences in mortality were not observed in the clinical evidence review.

We identified a need for more biologic-attributable evidence specifically around subpopulations and aspects of treatment responders that are conducted in the United States. While NICE has conducted extensive research on asthma biologics, such as mepolizumab and reslizumab,[28,103] the patient populations in their reports are based on the United Kingdom, not the United States, which limits the potential adaptability of our model.

We did not evaluate subpopulations such as those with income or ethnic disparities due to a lack of clinical evidence in these subgroups.

Finally, this analysis focused on estimating the long-term cost effectiveness of biologics within the asthma target population included in this review. Comorbidities associated with asthma were indirectly included within the asthma populations studied, and thus are included in the cost-effectiveness findings. However, specific subpopulations that included one or more comorbidities were not pre-specified for additional cost-effectiveness scenarios due to a lack of available evidence.

Conclusions

In conclusion, the findings of our analysis suggest that the biologic agents of focus for this review provide gains in quality-adjusted survival over standard of care alone. With the evidence available at this time, these biologic agents seem to be priced higher than the modeled benefits over a lifetime time horizon at commonly accepted cost-effectiveness thresholds. The findings were not sensitive to traditional sensitivity or scenario analyses but were most favorable in scenarios associated with long-term biologic treatment for responders or biologic initiation in the subgroup of chronic oral corticosteroid users. Evidence is needed to support or refute these scenario value projections. Higher value care is more likely to be achieved through careful patient selection and continued biologic therapy for only treatment responders.

5. Potential Other Benefits and Contextual Considerations

Table 5.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to standard therapy with high dose ICS and LABA there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to standard therapy with high dose ICS and LABA there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

The five biologics are all parenteral, which may impact the acceptability and long-term adherence to therapy. Four are delivered subcutaneously and one (reslizumab) is given by IV infusion. Only dupilumab is approved for self-injection. All of the other drugs require a visit to a medical center for each dose for administration by a health care professional.

In addition, the dosing schedule varies between the drugs, which may also impact acceptability to patients and long-term adherence. Dupilumab is given every two weeks, omalizumab is given every two to four weeks, mepolizumab and reslizumab are given every four weeks, and after the first three doses, benralizumab is given every eight weeks.

Dupilumab, in particular, offers a new mechanism of action. It is the first drug to target the IL-4 and IL-13 pathways in type 2 asthma.

There is limited evidence in the studies to date, but patients with severe asthma often miss school or work due to their asthma and even if present, may be less alert due to poor sleep or ongoing shortness of breath. All five biologics have the potential to improve this aspect of a patient's life.

5.2 Contextual Considerations

Asthma is a life-long disease and for children suffering from severe, poorly controlled asthma, the disease may impact the entire trajectory of their lives.

All the biologic interventions manipulate the immune response of patients and the long-term implications of such manipulation remain unclear.

6. Value-Based Price Benchmarks

Our value-based benchmark annual prices for the five asthma biologics are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For all considered biologics, the discounts required to meet both threshold prices are greater than their current discount from WAC.

Table 6.1 Value-Based Benchmark Prices of Asthma Biologics in the Treatment of Moderate to Severe Uncontrolled Asthma

Intervention	Annual WAC	Annual Price at $100,000 per QALY Threshold	Annual Price at $150,000 per QALY Threshold	Discount from WAC Required to Achieve Threshold prices
Omalizumab	$39,048	$9,000	$13,300	66% to 77%
Mepolizumab	$37,293	$9,200	$13,400	64% to 75%
Reslizumab	$31,637	$6,500	$10,400	67% to 80%
Benralizumab	$30,889*	$8,300	$11,900	62% to 73%
Dupilumab	$38,110‡	$10,100	$14,300	62% to 73%

*Assuming 6.5 doses per year, year-two onward since year-one has additional loading doses.

‡Assuming 26 doses per year, year-two onward since year-one has an additional loading dose.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab in its indicated population for asthma: adults and children twelve years of age and older with uncontrolled, moderate to severe asthma in the US. We used the WAC, net price, and the three threshold prices for dupilumab in our estimates of budget impact. We did not include omalizumab, mepolizumab, reslizumab or benralizumab in our calculations since they have all already been approved and have been in use in the US marketplace for close to a year, or more.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total net cost of using dupilumab rather than relevant existing therapy (SoC and other biologics) for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

As stated previously, the potential budget impact analysis included adults and children six years of age and older with persistent moderate to severe uncontrolled asthma in the US. We applied the CDC-reported asthma prevalence (8.3% among all US adults and children in 2016) to the 2018-2022 projected US population 12 years and older, to find the average number of patients with asthma.[104,105] We then applied the prevalence of persistent asthma, 64.8% in adults and 60.3% in children, to further narrow the population to reflect our target population.[106,107] While there exist estimates for severe asthma among those with persistent asthma, there aren't any robust published estimates on the percentage of population with moderate to severe asthma among those with persistent disease. We thus assumed that those on medications for long-term control comprised the moderate to severe group and hence applied these CDC reported estimates (39% in adults and 40.2% in children) to the persistent asthma population to derive the population with moderate to severe asthma.[108] In their review of asthma prevalence, disease burden and treatment options, Peters et al. reported that 20% of patients with severe asthma had uncontrolled asthma.[109] We applied this estimate more broadly to the moderate to severe asthma population, to arrive at an estimate of approximately 1.2 million patients over five years, or approximately 237,000 patients each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[110] and have been recently updated. The intent of our revised approach to budgetary impact is to

document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

To estimate potential budget impact, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that dupilumab would take market share from other biologics and non-biologic SoC. We found recent estimates on market share among biologics in asthma treatment (reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2% and omalizumab – 74.9%)[a], as well as the proportion of patients with moderate to severe asthma on biologics (27%) based on a manufacturer-sponsored survey in that patient group.[111,112] As the uptake of dupilumab among the incident target population or among patients currently on treatment for uncontrolled moderate to severe asthma remains unknown, we estimated the percentage of patients on the current treatment mix that could be displaced to dupilumab before the budget impact threshold is reached. Of course, this percentage need not reflect real-world uptake, especially in the presence of existing and established biologics in the asthma treatment paradigm.

7.3 Results

Table 7.1 illustrates the per-patient budget impact calculations, based on WAC ($38,110 per year), net price ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($14,300 per year, $10,140 per year, and $5,980 per year, respectively) compared to current treatment mix.

Table 7.1. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$46,059	$38,912	$22,127	$17,945	$13,764
Current Treatment Mix*	$44,651				
Difference (Dupilumab – Current Treatment Mix)	$1,408	($5,738)	($22,524)	($26,705)	($30,887)

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*27% of target population on biologics and 73% on standard of care. Market share among biologics: reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2%, and omalizumab – 74.9%

() – Cost-saving

[a] Note: This information is an estimate derived from the use of information under license from the following IQVIA information service: IQVIA US Defined Daily Doses (DDD) data for the period July 2018. IQVIA expressly reserves all rights, including rights of copying, distribution and republication.

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $1,400 per year. Average potential budgetary impact at dupilumab's net price resulted in cost-savings of approximately $5,700 per patient annually. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug were estimated to be cost saving, ranging from approximately $22,500 per patient in savings using the annual price to achieve $150,000 per QALY to approximately $30,900 per patient in savings using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold. It is important to note that these findings are versus a population-level treatment mix of biologics and SoC. Against just SoC alone, using dupilumab will result in greater budget impact at both the per patient and the population level across the five price points (WAC, discounted WAC, prices to reach willingness-to-pay [WTP] thresholds of $50,000, $100,000 and $150,000 per QALY).

At dupilumab's WAC, 91% of the eligible population could be treated before the total budget impact exceeds the ICER annual budget impact threshold. At its net price and prices to reach the cost-effectiveness thresholds between $50,000 and $150,000 per QALY, the total population budget impact resulted in cost-savings and the entire population could be treated.

7.4 Access and Affordability

As illustrated in the budget impact analysis, treating the entire patient population eligible for treatment with dupilumab at the net price and prices to reach commonly accepted WTP thresholds resulted in net savings. Additionally, at dupilumab's WAC, just over 90% of the entire eligible population could be treated each year without the total budget exceeding the ICER budget impact threshold. At the November 29, 2018 public meeting, the consensus among stakeholders was that uptake of dupilumab would likely not threaten access and affordability, given current market competition and dupilumab's anticipated net price for this indication. As such, ICER is not issuing an access and affordability alert at this time. However, all stakeholders should closely monitor the use of dupilumab for uptake exceeding expectations, along with any unprecedented net price increase.

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 29, 2018 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of biologic therapies for the treatment of asthma. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 6:06), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to biologic treatments for asthma. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

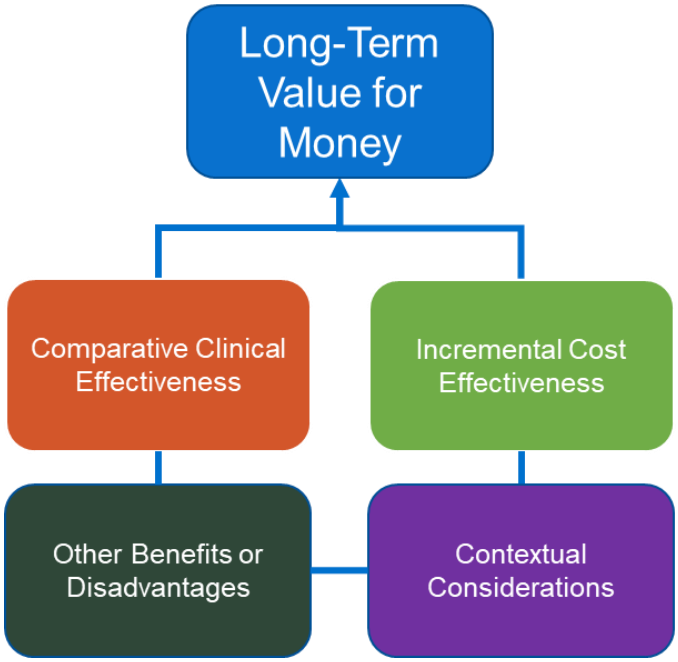
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant 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 of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

For patients ≥ 12 years with uncontrolled, moderate to severe asthma, and eosinophilic phenotype:

1. **Is the evidence adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care (ICS plus at least one additional controller medication)?**

Yes: 12 votes	No: 3 votes

A majority of the CEPAC Council voted that the evidence was adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care. Council members who voted in the affirmative stated that quality of life improvements weighed heavily on their votes. Additionally, Council members considered reduction in the use of OCS for patients treated with dupilumab as an important clinical outcome of benefit to patients given the significant side effects of long-term steroid use. Finally, the relative risk reduction in exacerbation events was substantially larger for patients treated with dupilumab as compared to those receiving standard of care and Council members cited this absolute reduction as a clear indication of positive net health benefit.

For patients ≥ 12 years with uncontrolled, severe asthma, and eosinophilic phenotype:

2. Is the evidence adequate to distinguish the net health benefit *among* mepolizumab, reslizumab, and benralizumab?

Yes: 1 vote	***No: 14 votes***

A majority of the Council determined that the evidence was inadequate to distinguish the net health benefit among mepolizumab, reslizumab, and benralizumab. One Council member who voted in the negative emphasized that the lack of head-to-head trials and heterogeneity in trial populations precluded their ability to distinguish between agents. Another Council member noted that four out of five network meta-analyses conducted on these three biologics (including the one performed by ICER) did not find statistically-significant differences among them and agreed with the point made by the clinical experts present at the meeting that the biologics are essentially interchangeable in clinical practice.

IF NO…

3. Is the evidence adequate to distinguish the net health benefit *between* dupilumab and these three treatments?

Yes: 0 votes	***No: 15 votes***

The Council unanimously judged that the evidence was inadequate to distinguish the net health benefit between dupilumab and the three agents listed above. Several Council members cited the lack of head-to-head trials, and the heterogeneity between trial populations.

4. Is the evidence adequate to distinguish the net health benefit *between* omalizumab and these three treatments?

Yes: 0 votes	***No: 15 votes***

The Council voted unanimously that the evidence was inadequate to distinguish the net health benefit between omalizumab and mepolizumab, reslizumab, and benralizumab. Once again, the lack of head-to-head trials made distinguishing between treatments difficult. One Council member asked why there didn't seem to be a correlation between time on the market, and the amount and quality of evidence for these biologics? Dr. Jeff Tice generally agreed that time on the market did not correlate with better evidence but stipulated that a drug's safety profile was the expectation. The clinical experts agreed and confirmed that the risk for unexpected harms from omalizumab or mepolizumab was low given the longevity of each. Even so, Council members were unconvinced that this one piece of evidence was enough to distinguish these biologics and voted the evidence was inadequate to distinguish.

5. In the treatment of patients ≥ 12 years with moderate to severe asthma, does dupilumab offer one or more of the following potential other benefits or disadvantages compared to best usual care without biologic treatment?

Dupilumab offers reduced complexity that will significantly improve patient outcomes.	3/15
Dupilumab will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	0/15
Dupilumab will significantly reduce caregiver or broader family burden.	6/15
Dupilumab offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	8/15
Dupilumab will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	7/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3/15

Three Council members judged that dupilumab offers reduced complexity, noting that if treatment leads to reduced OCS use, a patient's treatment regimen will be simplified. Those who did not vote for this option argued that adding a biologic to standard of care inherently increases the complexity of treatment. Council members also discussed adherence as another important benefit. Clinical experts present at the meeting noted that adherence rates have been shown to be very high with biologics but under 60% with standard of care. Both the ability to reduce OCS use and the potential for high adherence led Council members to vote dupilumab would decrease caregiver burden and improve patients' ability to return to work and/or their overall productivity. Council members also acknowledged that dupilumab has a different mechanism of action from the other biologics, so it could allow for the successful treatment of many patients for whom other treatments have failed. No Council members voted that this drug would reduce health disparities, noting that this disease disproportionately impacts people of color and families with low socioeconomic status and those individuals are also the least likely to seek treatment.

6. Are any of the following contextual considerations important in assessing the long-term value for money of dupilumab versus best usual care without biologics?

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/15
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12/15
This intervention is the first to offer any improvement for patients with this condition.	0/15
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	8/15
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	11/15
There are additional contextual considerations that should have an important role in judgments of the value of this intervention:	3/15

Council members acknowledged the high burden of disease asthma presents to patients with severe asthma. They thanked the patients who delivered public comments for sharing their stories and painting a picture of what it's like to live with what can be a debilitating and life-threatening condition. The majority voted that dupilumab is intended to care for patients with a condition of high severity and a high lifetime burden of illness. Due to the availability of multiple treatments available for patients with severe asthma, no Council members voted that dupilumab was the first to offer improvements to this patient population. A majority of the Council members felt that there is uncertainty about the long-term benefits of dupilumab, citing the lack of long-term trial evidence. Similarly, eight out of the 15 Council members voted that there was uncertainty about the long-term risk of side effects, again noting the lack of evidence.

7. Are there important and distinctive other benefits or disadvantages, or unique contextual considerations that apply to any of the other biologic treatments for their labeled population?

Council members noted that dupilumab can be self-administered at home by the patient, whereas the other biologics in the review required an office visit for administration. Conversely, one Council member commented that while self-administration presents an opportunity for increased access, it also risks causing a decrease in adherence. Lack of adherence is not only dangerous for patients but creates significant waste in health-care spending, particularly in this case due to the high cost of the drug. Many Council members acknowledged that self-administration presents a trade-off, but all agreed the increased ease of self-administration was a net-positive for patients.

Long-term Value for Money Votes

As described in ICER's recent update to its **value assessment framework**, questions on "long-term value for money" are subject to a value vote only when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case"

analysis. As shown in the Evidence Report, the estimates for all five biologics exceed the higher end of the range and thus all interventions are deemed "low value" without a vote of the panel.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on biologics for treatment of asthma to policy and practice. The policy roundtable members included two patient representatives, two clinical experts, two payers, and five representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1. Policy Roundtable Members

Name	Title and Affiliation
Mario Castro, MD, MPH	Professor of Medicine, Pediatrics, and Radiology, Washington University School of Medicine
David Evan	Senior Director, Strategic Brand Marketing, Teva
Marsha Fisher, MD, FACOG	Medical Operations Director, Anthem BCBS of Missouri
Mark S. Forshag, MD, MHA	US Medical Expert – Respiratory, GlaxoSmithKline
Jeremy Fredell, PharmD, BCPS	Director, Trend Solutions - Drug Trend & Formulary, Express Scripts
Benjamin Kramer, MD	Vice President, Immunology and Ophthalmology, US Medical Affairs, Genentech
Andreas Kuznik, PhD	Senior Director, Health Economics and Outcomes Research, Regeneron
Donna J. Matlach, DMin, MM, CDA	Patient Advocate; Board Member, Allergy and Asthma Network
Kenny Mendez, MBA	President and CEO, Asthma and Allergy Foundation of America
Kaharu Sumino, MD, MPH	Staff physician, Saint Louis VA Medical Center; Associate Professor of Medicine, Washington University School of Medicine
Frank Trudo, MD, MBA	Vice President, US Medical Affairs, Respiratory, AstraZeneca

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

To provide fair value to patients and the health system, manufacturers should lower the prices of biologic therapies for asthma so that they align with the added value they bring to patients.

The price increases observed for omalizumab and the launch prices of more recent biologics do not align with usual standards for value that reflect a price proportionate to the added benefits

experienced by patients. There is no a priori reason why monoclonal antibody therapy for asthma should command exceptional pricing. There has been extensive experience with the development and manufacturing of monoclonal antibody therapies for many indications over the past two decades. Indeed, some monoclonal antibodies are sold for less than $3,000 a year (denosumab) and maintain profitability for their manufacturers.

Given the high clinical burden borne by patients with uncontrolled, severe asthma, high prices for these effective drugs impose an unfair burden on patients and are likely to trigger greater constraints by insurers on access. Manufacturers should bring lower prices to the negotiating table with insurers in return for broader access for patients who can benefit from these important treatments.

Plan Sponsors

Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing excellent access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.

Current approaches to insurance coverage often rely on negotiations for preferential formulary status in return for lower net prices. This approach is one of the few tools that plan sponsors have to seek any leverage in controlling costs, but it can create complexity and burdens for clinicians and patients. Plan sponsors should work with payers to develop benefit design and negotiation platforms that can provide a clear pathway for drugs that are priced fairly to be covered with minimum prior authorization controls. In addition, fair pricing as established in comparison to external, independent assessment, should be matched with low out-of-pocket requirements for patients.

Payers

Given that, to date, manufacturers have not priced biologics for asthma at a value-based level, payers are likely to offer preferential formulary status in return for lower prices. For many patients the evidence is not adequate to determine which drug would be superior as a first option, therefore it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients.

Until recently, patients and clinicians had limited options when background inhaler therapy was not able to provide adequate control for patients with severe eosinophilic asthma. Now, in addition to omalizumab, there are four options, not all of which have identical indications, but which have similar mechanisms of action and therefore offer options for many patients. Clinical experts involved in the ICER review expressed the opinion that it was reasonable for payers to establish step therapy policies as long as patients who did not respond on a first-step option would not face

significant barriers in switching to another option. The four biologics currently available for uncontrolled, moderate to severe, eosinophilic asthma appear to offer similar improvements in asthma exacerbations and quality of life. There are no head to head clinical trials of the agents and indirect treatment comparisons have not identified significant differences between the biologics. Given the lack of biomarkers that indicate that one agent is more likely than the others to benefit an individual patient, step therapy is a reasonable option. However, even at the first step, there should be an easy pathway for appeal for alternative agents. For example, weight-based dosing, which is only used with reslizumab, may be appropriate for obese patients who fail initial therapy.

In addition to step therapy, payers will develop prior authorization criteria to ensure that prescriptions are covered only for appropriate patients and that use of these expensive medications is prudent. Potential considerations regarding elements of prior authorization criteria for the biologics other than omalizumab are shown below:

Patient eligibility

Patients who meet the FDA indications for mepolizumab, reslizumab, benralizumab, and dupilumab (other than in patients on chronic OCS) have uncontrolled, moderate to severe eosinophilic asthma.

1. *Diagnosis of asthma*: Clinical experts suggested that as many as 30% of patients referred to specialty asthma providers are found not to have asthma. Therefore, a confirmation of asthma is reasonable. Clinical guidelines suggest that the diagnosis of asthma should be confirmed with spirometry: a pre-bronchodilator FEV1 < 80% predicted and FEV1 reversibility of at least 12%.
2. *Uncontrolled*: The definition of uncontrolled can be left to the discretion of the clinician but many payers will establish some empirical threshold. This criterion could be set at a number of exacerbations in the past 12 months, but it may ideally reflect both the number and severity of asthma exacerbations. For example, uncontrolled asthma could be defined as at least two exacerbations requiring oral corticosteroids or at least one hospitalization due to an asthma exacerbation. In Europe, the criteria for use of some of these biologics requires at least four exacerbations in the prior year, reflecting greater relative and absolute benefits in the population of patients with greater numbers of exacerbations.
3. *Severe*: Looking to authoritative guidelines, payers may consider requiring that patients meet the criteria for Global Initiative for Asthma (GINA) step 5: treatment with high dose ICS and another controller agent for at least six months. Ensuring that patients have been receiving excellent background care prior to consideration of biologics will ensure that patients are not started on biologics unnecessarily.
4. *Eosinophilic phenotype*: Eosinophilia could be defined as eosinophil levels ≥ 150, 300, or 400 cells/µl with greater relative and absolute benefits for higher eosinophil levels. Given the high costs and low value of the biologics, some clinical experts felt that it would be reasonable to require levels of at least 300 eosinophils/µl within the prior year. Note, when the FDA indicated these drugs for eosinophilia, an exact cut-point was not defined.

Continuation criteria

Given that the effectiveness of the biologics is usually apparent within six months of use, payers should work with clinicians to assess treatment response after six months of therapy.

Clinical experts indicated that 6 months of treatment was sufficient to assess response. Measures commonly used by asthma experts to assess response include an improvement in the ACT of at least three points or an improvement in FEV1 of at least 100 ml.

Combination therapy

Combination therapy with two or more biologics should not be covered except under exceptional circumstances. There is no evidence that combinations of any of the five biologic therapies improve outcomes.

Provider criteria

It would be reasonable for payers to require that biologic therapy prescribing be restricted to specialists (pulmonary specialist/allergy and immunology specialist) or by primary care physicians only after consultation with a specialist.

Since biologic therapies for asthma are expensive and as many as 30% of patients referred to specialist with severe asthma do not have asthma as the underlying diagnosis, payers may wish to consider requiring diagnosis by an asthma specialist to confirm the diagnosis of asthma and to ensure the optimal delivery of non-biologic therapies. However, consideration should be given to access to care in geographic regions where specialists are not readily accessible. In that case, specialist consultation may suffice for coverage of therapy.

The process for authorization of biologic therapies for asthma should be clear and efficient for providers.

Patients and providers reported delays of several months in obtaining authorization decisions for biologic therapies. Specialists in asthma spoke of the need for a full-time employee primarily to assist with authorization and continuation therapy for biologic therapies for asthma. They also reported that some specialists refer patients to severe asthma clinics solely for assistance with obtaining authorization. Insurers should implement streamlined processes that are evidence-based and timely to ensure that patients for whom biologic therapy is appropriate are able to begin treatment in a timely manner.

When patients change insurance, coverage for their biologic should be continued to avoid worsening of asthma control.

Patients should not be denied effective therapy because of a change of insurance. However, it would be reasonable to require documentation of the effectiveness of therapy for continuation of the biologic after six months.

Payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their ICS or other long-acting controller medications during treatment with the biologic.

One of the benefits of biologic therapy for asthma is improved control, which may allow for de-intensification of therapy. A reduction in the use of oral corticosteroids, high dose inhaled corticosteroids, and rescue medications are markers of the effectiveness of the biologic and should not be viewed as a reason to stop therapy. To date, there is no evidence supporting ongoing efficacy once a biologic therapy is withdrawn.

Manufacturers, insurers, and governments should work to remove barriers to indication-specific pricing.

Indication-specific pricing would be an important innovation for drugs that offer dissimilar value for different indications. Many of the biologics have FDA approval for other indications. Some, such as dupilumab, meet typical willingness to pay thresholds for one indication (atopic dermatitis), but not for asthma. The "Medicaid best price" provision may limit innovation in pricing that separately reflects the value in multiple indications, formularies may not be set up in a way that allows for differential tiering based on indication, insurers may have difficulty tracking indication-specific pricing without separate drug codes and/or brand names by indication, and anti-kickback laws may limit the rebates that manufacturers are able to include in these arrangements [ICER ISP White Paper, 2016]. Alternative approaches to fair pricing need to be developed to facilitate better alignment of prices with patient benefit across indications. As an example, if utilization tracking is relatively straightforward, insurers could negotiate a "weighted" rebate across indications based on the value-based price in each indication adjusted by expected or actual utilization in each indication. As a final option, manufacturers may consider rebranding treatments by indication to facilitate indication-specific prices.

Specialty Societies

Specialty societies should develop a clear definition of response to biologic therapy.

Clinical guidelines should include both the time frame for assessing response to biologic therapies for asthma and the criteria for response. Suggested criteria that could serve as a starting point include an evaluation after six months of therapy and an improvement of three points or more on

the Asthma Control Test (ACT) or an improvement of FEV1 at least 100 ml for an adequate response. Non-responders should not continue the biologic but could be considered for another biologic.

Because of pervasive cost issues, pulmonologists, allergists and their specialty societies should advocate for prices to be better tied to the clinical benefits that drugs bring to their patients.

Specialists recognize the financial impact that these expensive drugs have on their patients. They need to include cost as part of shared decision-making with patients and advocate for lower prices on behalf of their patients.

Researchers

Head to head comparisons of the biologic therapies for asthma are essential.

Ideally, an organization, such as PCORI, should support a pragmatic comparative clinical trial for the four biologics with an indication for uncontrolled eosinophilic asthma. Given the low likelihood of that happening in the short term, there should be support for a large, prospective observational study capturing data on patients eligible for these biologics that would allow for state-of-the-art methods, such as propensity score adjusted analysis, to compare the clinical effectiveness of the five biologic therapies.

Better instruments to measure quality of life need to be developed.

Under the leadership of the FDA, companies should develop and validate a novel quality of life measure that captures benefits that matter to patients and maps to standard measures of utility such as the EQ5D.

Regulators

The FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.

The heterogeneity across the trials of asthma biologics both in the instruments used to assess asthma exacerbations and quality of life and the timing of their assessment preclude high quality comparative effectiveness studies between biologics. The FDA should work with specialty societies and manufacturers to update the guidance for asthma trials to facilitate comparisons between active therapies.

Active comparators should be the standard in pivotal trials.

Given the large body of evidence that that treatment of uncontrolled, severe asthma with biologic agents decreases asthma exacerbations and increases quality of life, it is unethical to continue to perform placebo-controlled trials in high-risk patients. Requiring an active comparator in clinical trials would also improve patient and clinician understanding of the relative benefits and risks of available treatment options.

****

This is the second ICER review of asthma treatments.

References

1. Centers for Disease Control and Prevention. National Center For Health Statistics Faststats. 2017; https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed 05/15, 2018.
2. Centers for Disease Control and Prevention. ASTHMA FACTS - CDC's National Asthma Control Program Grantees. 2013; https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf. Accessed 05/15, 2018.
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. Schatz M, Rosenwasser L. The allergic asthma phenotype. *J Allergy Clin Immunol Pract.* 2014;2(6):645-648; quiz 649.
5. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol.* 2015;15(1):57-65.
6. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *American journal of respiratory and critical care medicine.* 2010;181(4):315-323.
7. Food and Drug Administration (FDA). Xolair Label. 2007; https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Accessed 05/15, 2018.
8. Food and Drug Administration (FDA). Nucala Label. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed 05/15, 2018.
9. Food and Drug Administration (FDA). Cinquair Label. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed 05/15, 2018.
10. Food and Drug Administration (FDA). Fasenra Label. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed 05/15, 2018.
11. Food and Drug Administration (FDA). Dupixent Label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Accessed 11/01/2018, 2018.
12. Asthma and Allergy Foundation of America. My Life With Asthma: Survey Overview. 2017. www.aafa.org/media/my-life-with-asthma-in-2017-survey-findings-report.pdf.
13. American Academy of Allergy Asthma & Immunology. Choosing Wisely. 2012; http://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunology-spirometry-for-asthma-diagnosis-and-management/. Accessed September 24, 2018.
14. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014(1):CD003559.
15. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev.* 2017;9:CD010834.
16. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *The New England journal of medicine.* 2018;378(26):2486-2496.
17. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *The New England journal of medicine.* 2018;378(26):2475-2485.

18. Regeneron Pharmaceuticals Inc. and Sanofi. Statement at Midwest CEPAC Public Meeting. In:November 29, 2018.
19. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *The Journal of allergy and clinical immunology.* 2013;132(2):485-486.
20. Busse W, Chupp G, Nagase H, et al. Anti-IL5 treatments in severe asthma by blood eosinophil thresholds: indirect treatment comparison. *The Journal of allergy and clinical immunology.* 2018.
21. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 Suppl B:25-31; discussion 33-27.
22. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *The American review of respiratory disease.* 1992;145(6):1321-1327.
23. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *The European respiratory journal.* 2002;19(3):398-404.
24. Bae YJ, Kim YS, Park CS, et al. Reliability and validity of the St George's Respiratory Questionnaire for asthma. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2011;15(7):966-971.
25. Nelsen LM, Vernon M, Ortega H, et al. Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. *Respir Med.* 2017;128:42-49.
26. Drazen JM, Harrington D. New Biologics for Asthma. *The New England journal of medicine.* 2018;378(26):2533-2534.
27. ICER. Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks. *Institute for Clinical and Economic Review.* 2016.
28. National Institute for Health and Care Excellence. Mepolizumab for treating severe refractory eosinophilic asthma. Technical appraisal guidance TA431. In: NICE, ed. London2017.
29. de Vries F, Setakis E Fau - Zhang B, Zhang B Fau - van Staa TP, van Staa TP. Long-acting {beta}2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *The European respiratory journal.* 2010;36(3):494-502.
30. 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.
31. Levy M, Andrews R, Buckinghma R, et al. Why asthma still kills: The national review of asthma deaths (NRAD). In: Physicians RCo, ed. London: Royal College of Physicians; 2014.
32. 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.
33. Anarella JP, Wagner VL, McCauley SG, Mane JB, Waniewski PA. Eliminating Disparities in Asthma Care: Identifying Broad Challenges in Quality Improvement. *American journal of medical quality : the official journal of the American College of Medical Quality.* 2017;32(6):598-604.
34. Mitchell SJ, Bilderback AL, Okelo SO. Racial Disparities in Asthma Morbidity Among Pediatric Patients Seeking Asthma Specialist Care. *Academic pediatrics.* 2016;16(1):64-67.
35. Zhang Q, Lamichhane R, Diggs LA. Disparities in emergency department visits in American children with asthma: 2006-2010. *J Asthma.* 2017;54(7):679-686.
36. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining Racial Disparities in Child Asthma Readmission Using a Causal Inference Approach. *JAMA pediatrics.* 2016;170(7):695-703.

37. Cazzola M, Calzetta L, Matera MG, Hanania NA, Rogliani P. How does race/ethnicity influence pharmacological response to asthma therapies? *Expert opinion on drug metabolism & toxicology.* 2018;14(4):435-446.
38. DePriest K, Butz A. Neighborhood-Level Factors Related to Asthma in Children Living in Urban Areas. *The Journal of school nursing : the official publication of the National Association of School Nurses.* 2017;33(1):8-17.
39. Hughes HK, Matsui EC, Tschudy MM, Pollack CE, Keet CA. Pediatric Asthma Health Disparities: Race, Hardship, Housing, and Asthma in a National Survey. *Academic pediatrics.* 2017;17(2):127-134.
40. Louisias M, Phipatanakul W. Managing Asthma in Low-Income, Underrepresented Minority, and Other Disadvantaged Pediatric Populations: Closing the Gap. *Current allergy and asthma reports.* 2017;17(10):68.
41. Buchman AL. Side effects of corticosteroid therapy. *J Clin Gastroenterol.* 2001;33(4):289-294.
42. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018; https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 06/11, 2018.
43. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *The New England journal of medicine.* 1990;323(15):1033-1039.
44. Wardlaw AJ, Brightling CE, Green R, Woltmann G, Bradding P, Pavord ID. New insights into the relationship between airway inflammation and asthma. *Clin Sci (Lond).* 2002;103(2):201-211.
45. Woolf S. *An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale.*: Agency for Health Care Policy and Research;1994.
46. Net MH. Clinical Edit Criteria. 2017; https://dss.mo.gov/mhd/cs/pharmacy/pdf/Respiratory-Monoclonal-Antibodies-Clinical.pdf.
47. Wellcare I. Perscription Drug Plans. 2018; https://wellcare.destinationrx.com/PlanCompare/Consumer/Type1/2018/Compare/ComparePlans. Accessed August 27 2018.
48. Aetna. Mepolizumab (Nucala). 2018; http://www.aetna.com/cpb/medical/data/800_899/0897.html. Accessed Aug 27, 2018.
49. Aetna. Reslizumab (Cinqair). 2018; http://www.aetna.com/cpb/medical/data/900_999/0907.html. Accessed Aug 28, 2018.
50. Aetna. Benralizumab (Fasenra). 2018; http://www.aetna.com/cpb/medical/data/900_999/0925.html. Accessed Aug 27, 2018.
51. Cigna. Cigna Drug and Biologic Coverage Policy: Interleukin (IL)-5 Antagonists: Mepolizumab and Reslizumab. 2017; https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_1608_pharmacycoverageposition_IL5_antagonists.pdf. Accessed Aug 27, 2018.
52. Cigna. Cigna Drug and Biologic Coverage Policy: Omalizumab. 2018; https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_4026_pharmacycoverageposition_xolair.pdf. Accessed Aug 27, 2018.
53. Aetna. Specialty Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Perscription Drug Plan. 2017; http://www.aetna.com/products/rxnonmedicare/data/2017/RESP/Xolair.html. Accessed August 27, 2018.
54. US Department of Health and Human Services NIoH, National Heart, Lungs, and Blood Institute, . *Guidelines for the Diagnosis and Management of Asthma.* October 2007 2007.
55. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. In:2017.

56. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
57. Higgins JPG, S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions* Version 5.1.0 ed: The Cochrane Collaboration; 2008.
58. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.
59. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
60. Agency for Healthcare Research and Quality (AHRQ). U.S. Preventive Services Task Force Procedure Manual. 2008; https://www.uspreventiveservicestaskforce.org/Home/GetFile/6/7/procmanual/pdf.
61. National Asthma Education and Prevention Program. Expert Panel Report 2 (EPR-2): Guidelines for the Diagnosis and Management of Asthma. *NIH Publication No 97-4051.* 1997.
62. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet (London, England).* 2016;388(10056):2115-2127.
63. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England).* 2016;388(10056):2128-2141.
64. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *The Lancet Respiratory medicine.* 2016;4(7):549-556.
65. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005;60(3):309-316.
66. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet (London, England).* 2012;380(9842):651-659.
67. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England journal of medicine.* 2011;364(11):1005-1015.
68. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics.* 2001;108(2):E36.
69. Siergiejko Z, Swiebocka E, Smith N, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. *Current Medical Research and Opinion.* 2011;27(11).
70. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *The New England journal of medicine.* 2014;371(13):1189-1197.
71. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *The New England journal of medicine.* 2017;376(25):2448-2458.
72. 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.
73. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Annals of Allergy, Asthma & Immunology.* 2018;118(2):220-225 (Print).

74. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201).* 04/2013 2013.
75. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Techonlogy Assessment.* 2013;17(52).
76. 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.
77. Campbell JD, B. MR, 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(2325-6621 (Electronic)).
78. 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.* 2014;17(8):772-782.
79. Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. *Allergy.* 2008;63(12):1581-1592.
80. 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.* 2016;19(4):319-355.
81. Reddel H, Taylor D, Bateman E, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American journal of respiratory and critical care medicine.* 2009;180(1):59-99.
82. Chipps BE, Zeiger RS, Luskin AT, et al. Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO. 2017(1534-4436 (Electronic)).
83. Starkie H, Briggs A, Chambers M, Jones P. Predicting EQ-5D values using the SGRQ. *Value in Health.* 2011;14(2):354-360.
84. Tsuchiya A, Brazier J, McColl E. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. *White Rose Research Online.* 2002.
85. Lefebvre P, Duh MS, Lafeuille MH, et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Current medical research and opinion.* 2017;33(1):57-65.
86. Bousquet J, Cabrera P Fau - Berkman N, Berkman N Fau - Buhl R, 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(0105-4538 (Print)).
87. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *The New England journal of medicine.* 2014;371(13):1198-1207.
88. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet Respiratory medicine.* 2015;3(5):355-366.
89. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *The Lancet Respiratory medicine.* 2017;5(5):390-400.
90. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *The New England journal of medicine.* 2009;360(10):973-984.
91. 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.

92. Sutter Health Palo Alto Medical Foundation. Oral Corticosteroids. Accessed 06/15/2018, 2018.
93. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulmonary Medicine.* 2017;17(1):74.
94. Bureau of Labor Statistics. Consumer Price Index Historical Table, U.S. City Average, All items, 1982-84=100. https://www.bls.gov/regions/midwest/data/consumerpriceindexhistorical_us_table.pdf. Accessed 08/28/2018, 2018.
95. ICER. *ICER's Reference Case for Economic Evaluations: Principles and Rationale.* 07/26/2018 2018.
96. Centers for Medicare and Medicaid Services. Physician Fee Schedule Search. 2017; https://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx.
97. Asthma and Allergy Foundation of America (AAFA). Cost of Asthma on Society. 2018; http://www.aafa.org/page/cost-of-asthma-on-society.aspx. Accessed 08/24/18, 2018.
98. Bureau of Labor Statistics. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted. 2017; https://www.bls.gov/news.release/empsit.t19.htm. Accessed 08/22/18, 2018.
99. Genentech. Data on File.
100. Kim CH, Dilokthornsakul P, Campbell JD, van Boven JFM. Asthma Cost-Effectiveness Analyses: Are We Using the Recommended Outcomes in Estimating Value? *J Allergy Clin Immunol Pract.* 2018;6(2):619-632.
101. McQueen RB, Sheehan DN, Whittington MD, van Boven JFM, Campbell JD. Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. *PharmacoEconomics.* 2018.
102. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma. Technical appraisal guidance (TA278).* London, UK2013.
103. National Institute for Health and Care Excellence. Reslizumab for treating severe eosinophilic asthma. Technical appraisal guidance TA479. In: NICE, ed. London2017.
104. Most Recent Asthma Data. 2018. https://www.cdc.gov/asthma/most_recent_data.htm. Accessed Septemebr 15, 2018.
105. 2017 National Population Projections Datasets. 2018. Accessed September 15, 2018.
106. Asthma Severity among Adults with Current Asthma. 2015. https://www.cdc.gov/asthma/asthma_stats/severity_adult.htm. Accessed September 15, 2018.
107. Asthma Severity among Children with Current Asthma. 2015. https://www.cdc.gov/asthma/asthma_stats/severity_child.htm. Accessed September 15, 2018.
108. Use of long-term control medication among persons with active asthma. 2014. https://www.cdc.gov/asthma/asthma_stats/longterm_medication.htm. Accessed September 15, 2018.
109. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med.* 2006;100(7):1139-1151.
110. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.
111. Teva Pharmaceuticals. *IQVIA Data on File.* 2018.
112. Genentech. *Living with Moderate-to-Severe Persistent Asthma: Perspectives from Patients and Caregivers.* South San Francisco, CA: Genentech;2018.
113. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.

114. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy.* 2004;59(7):709-717.
115. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Annals of internal medicine.* 2011;154(9):573-582.
116. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma.* 2012;49(2):144-152.
117. Li J, Kang J, Wang C, et al. Omalizumab Improves Quality of Life and Asthma Control in Chinese Patients With Moderate to Severe Asthma: A Randomized Phase III Study. *Allergy, asthma & immunology research.* 2016;8(4):319-328.
118. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet (London, England).* 2016;388(10039):31-44.
119. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. 2016; https://CRAN.R-project.org/package=gemtc.
120. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy.* 2018;73(2):490-497.

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.

	#	Checklist item
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

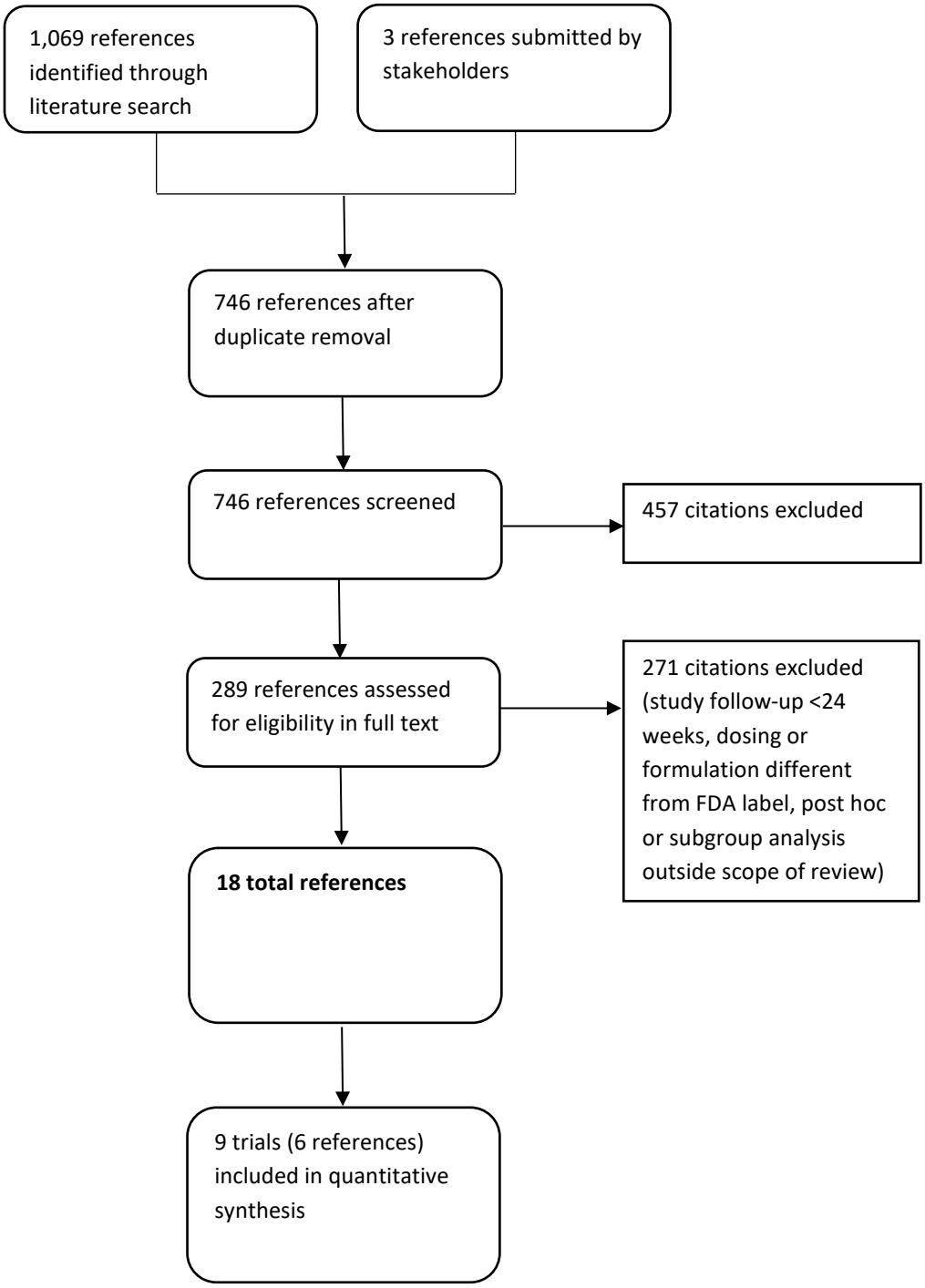
Table A2. Search Strategy of Medline and Cochrane Central Register of Controlled trials (via Ovid)

1	exp asthma/
2	asthma$.mp.
3	exp bronchial spasm/
4	bronchospas$.mp.
5	(bronch$ adj3 spasm$).mp.
6	exp bronchoconstriction/
7	bronchoconstrict$.mp.
8	(bronch$ adj3 constrict$).mp.
9	bronchial hyperreactivity/
10	respiratory hypersensitivity/
11	((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyper-sensitiv$ or hyperreactiv$ or hyper-reactiv$ or allerg$ or insufficien$ or hyperresponsive$ or hyper-responsive$)).mp.
12	or/1-11
13	omalizumab/
14	omalizumab.ti,ab.
15	(rhuMAB-E25* or Xolair*).ti,ab.
16	mepolizumab.ti,ab.
17	(nucala* or bosatria or sb-240563 or sb240563 or 90Z2UFOE52).ti,ab.
18	(reslizumab or cinqair or cinqaero or cinquil or DCP835 or DCP-835 or CEP38072 or CEP-38072 or SCH55700 or SCH-55700).ti,ab.
19	(benralizumab or fasenra or medi563 or medi-563).ti,ab.
20	(dupilumab or dupixent or regn 668 or regn668 or sar 231893 or sar231893).ti,ab.
21	or/13-20
22	12 and 21
23	(animals not (humans and animals)).sh.
24	22 not 23
25	limit 24 to english language
26	'clinical trial'.ti,ab.
27	'randomized controlled trial'.ti,ab.
28	'randomised controlled trial'.ti,ab.
29	randomi$ation.ti,ab.
30	'single blind'.ti,ab.
31	(double adj2 blind$).ti,ab.
32	placebo.ti,ab.
33	rct.ti,ab.
34	'random allocation'.ti,ab.
35	'randomly allocated'.ti,ab.
36	'allocated randomly'.ti,ab.
37	(allocated adj2 random$).mp.
38	or/26-37
39	((case adj2 study) or (case adj2 studies) or (case adj2 series) or (case adj2 report)).ti,ab.
40	38 not 39
41	40 and 25
Date of search: June 4, 2018	

Table A3. Search Strategy of EMBASE

#1	'asthma'/exp
#2	'asthm*'
#3	'bronchospasm'/exp
#4	'bronchospas*'
#5	bronch* NEAR/3 spasm*
#6	'bronchoconstriction'/exp
#7	bronchoconstrict*
#8	'bronchus hyperreactivity'/exp
#9	'respiratory tract allergy'/exp
#10	(bronch* OR respiratory OR airway$ OR lung$) NEAR/3 (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficien* OR hyperresponsiv)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'omalizumab'/exp
#13	'omalizumab':ti,ab
#14	'rhumab e25*':ti,ab OR xolair*:ti,ab
#15	'mepolizumab'/exp
#16	'mepolizumab':ti,ab
#17	nucala*:ti,ab OR bosatria:ti,ab OR sb240563:ti,ab OR 90z2ufoe52:ti,ab
#18	'reslizumab'/exp
#19	reslizumab:ti,ab OR cinqair:ti,ab OR cinqaero:ti,ab OR cinquil:ti,ab OR dcp835:ti,ab OR cep38072:ti,ab OR sch55700:ti,ab
#20	'benralizumab'/exp
#21	benralizumab:ti,ab OR fasenra:ti,ab OR medi563:ti,ab
#22	'dupilumab'/exp
#23	dupilumab:ti,ab OR dupixent:ti,ab OR regn668:ti,ab OR sar231893:ti,ab
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#11 AND #24
#26	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#27	'human'/exp
#28	#26 AND #27
#29	#26 NOT #28
#30	#25 NOT #29
#31	#30 AND [english]/lim
#32	#31 AND [medline]/lim
#33	#31 NOT #32
#34	'clinical trial':ti,ab
#35	'randomized controlled trial'
#36	'randomized controlled trial':ti,ab
#37	'randomised controlled trial':ti,ab
#38	'randomi$ation':ti,ab
#39	'single blind procedure'
#40	(single NEAR/2 blind*):ti,ab
#41	(double NEAR/2 blind*):ti,ab
#42	'double blind procedure'
#43	placebo:ti,ab
#44	rct:ti,ab
#45	(random* NEAR/3 allocat*):ti,ab
#46	random*:ti,ab
#47	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48	((case NEAR/2 stud*):ti,ab) OR ((case NEAR/2 report):ti,ab)
#49	#47 NOT #48
#50	#49 AND #33
#51	#50 AND ('editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#52	#50 NOT #51
Date of search: June 4, 2018	

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Biologic Therapies for Asthma



Appendix B. Previous Systematic Reviews and Technology Assessments

Prior Systematic Reviews, Meta-analyses, and Network Meta-analyses

There are numerous systematic reviews addressing one or more of the five biologics for asthma, though only one of the reviews compared dupilumab to other therapies. We summarize the most recent and prominent reviews below. The conclusions include evidence that mepolizumab is better, benralizumab is better, both reslizumab and dupilumab are better, or that there are no clear differences between the therapies. They vary in their inclusion criteria and the subgroup analyses performed. None of the NMAs included the recently published phase 3 trials of dupilumab. We summarize the most recent and prominent reviews below by year of publication.

Bourdin A, Husereau D, Molinari N, et al. Matching-Adjusted Indirect Comparison of Benralizumab versus Interleukin-5 Inhibitors: Systematic Review. *The European respiratory journal.* 2018.

The investigators performed an indirect comparison between benralizumab, reslizumab, and mepolizumab, which adjusts for differences in patient characteristics across trials. Benralizumab and reslizumab patient populations were too dissimilar to perform the analysis. The benefits of benralizumab and mepolizumab compared to placebo were nearly identical after adjustment.

Busse W, Chupp G, Nagase H, et al. Anti-IL5 treatments in severe asthma by blood eosinophil thresholds: indirect treatment comparison. *The Journal of allergy and clinical immunology.* 2018.

The investigators performed a network meta-analysis (NMA) based on the results of the Cochrane review of the three anti-IL-5 therapies, which is summarized below (Farne et al., 2017), with an updated search that identified two subgroup analyses and a pooled analysis not included in the Cochrane review. The NMA included 11 randomized trials with 3,723 patients who received the FDA indicated doses of the three drugs or matching placebo. The investigators performed subgroup analyses based on baseline eosinophil level and exacerbation history. They found that all treatments significantly reduced clinically significant asthma exacerbations and improved asthma control compared with placebo. Mepolizumab significantly reduced exacerbations and asthma control compared with both reslizumab and benralizumab. For example, in the subgroup of patients with baseline eosinophils ≥ 400 cells/µL, the rate ratio for mepolizumab versus reslizumab was 0.55 (95% CI 0.36 to 0.85) and the rate ratio for mepolizumab versus benralizumab was 0.55 (95% CI 0.35 to 0.87). They conclude that at the same baseline level of eosinophils, mepolizumab is superior to reslizumab and benralizumab.

Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M. Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis. *J Allergy Clin Immunol Pract.* 2018.

The investigators identified 11 studies, but only 4 had clinically relevant doses and outcomes at similar timepoints. They limited their analysis for reslizumab to patients with severe asthma and ≥2 exacerbations in the prior year with eosinophils ≥400 cells/µl and the analysis for benralizumab to patients with eosinophils ≥300 cells/µl. In their NMA, reslizumab had significantly greater improvements on the ACQ and AQLQ than benralizumab and a trend towards superiority of reslizumab for FEV1 and clinically significant asthma exacerbations. The investigators conclude that reslizumab may be more efficacious than benralizumab in patients with severe eosinophil asthma.

He LL, Zhang L, Jiang L, Xu F, Fei DS. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: A pairwise and Bayesian network meta-analysis. *International immunopharmacology.* 2018;64:223-231.

The investigators identified 21 placebo controlled randomized trials of mepolizumab (n=8), reslizumab (n=5) and benralizumab (n=7) for asthma. In their NMA there all 3 drugs significantly improved FEV1 and the AQLQ, but not exacerbations. There were no significant differences between the 3 drugs for any of the outcomes.

Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis. *Lung.* 2018;196(5):517-530.

The investigators used the frequentist NMA method to combine data from seven studies of mepolizumab, four of reslizumab, seven of benralizumab, two of dupilumab along with 6 studies of two drugs not included in our review (tralokinumab and lebrikizumab). The studies of dupilumab were short, phase 2 trials not included in the ICER review. The investigators found that all of the drugs except tralokinumab significantly improved FEV1, ACQ, and AQLQ, but only reslizumab and dupilumab had significant reductions in asthma exacerbation rates. There were no significant differences between drugs for any of the outcomes.

Cabon Y, Molinari N, Marin G, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. *Clinical & Experimental Allergy.* 2017;47(1):129-138.

The investigators identified 10 placebo controlled randomized trials (n=3421) of mepolizumab (n=4), reslizumab (n=4) and benralizumab (n=5) for asthma. They performed subgroup and sensitivity analyses by baseline eosinophil levels. They found that all 3 agents reduced asthma exacerbation rates by about 40% with slightly greater reductions when restricted to patients with eosinophil levels > 300 cells/µl. They found improvements in the ACQ that were significant, but

below the MCID as well as significant improvements in FEV1. The concluded that all 3 agents were effective, but that there was no clear superiority of one agent compared with another.

Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev.* 2017;9:CD010834.

The investigators identified 13 placebo controlled randomized trials (n=6000) of mepolizumab (n=4), reslizumab (n=4) and benralizumab (n=5) for asthma. They rated the randomized trials all to be low risk of bias and the evidence for all comparisons to be high quality. They found that all three therapies reduced clinically significant asthma exacerbations by about half in participants with severe eosinophilic asthma with modest improvements in health-related quality of life scores that did not reach the minimum clinically important difference for either the ACQ or the AQLQ. They found no excess in serious adverse events. Thus, they concluded that the evidence supports the use of any of the 3 agents in addition to standard of care in patients with severe eosinophilic asthma and poor control.

Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014(1):CD003559.

The investigators identified 25 trials including 6382 individuals randomized to omalizumab or placebo for moderate to severe allergic asthma. Omalizumab significantly reduced asthma exacerbations (RR 0.52, 95% CI 0.37-0.73)) as well as hospitalizations for asthma. Omalizumab patients were more likely to withdraw ICS completely (OR 2.50, 95% CI 2.0-3.1) and to have improvements in FEV1 (56.4 ml, 95% CI 16.8-96.0). Overall, there were fewer SAEs, but an increase in injection site reactions (OR 1.72, 95% CI 1.33-2.24). The authors concluded that omalizumab was effective at reducing asthma exacerbations and hospitalizations.

Selected Technology Assessments

National Institute for Health and Care Excellence (NICE)

NICE evaluated omalizumab for treating severe persistent allergic asthma in 2013. They recommend it as an option for treating severe persistent allergic IgE mediated asthma as an add-on to optimized standard therapy in people aged 6 and older who need continuous or frequent treatment with oral steroids (4 or more courses in the previous year). Optimized standard therapy includes inhaled high-dose corticosteroids, long-acting beta agonists leukotriene receptor antagonists, theophylline, oral corticosteroids and smoking cessation.

NICE evaluated mepolizumab for treating severe refractory eosinophilic asthma in 2017. It is recommended as an add on to optimized standard therapy for treating severe refractory eosinophilic asthma in adults. It is recommended in adults who have eosinophil count >300/µL in the previous 12 months and have had 4 or more asthma exacerbations requiring systemic

corticosteroids in the previous 6 months. An adequate response is defined as at least 50% fewer asthma exacerbations requiring steroids in the previous 12 months or a significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.

NICE evaluated reslizumab as an add on therapy for severe eosinophilic asthma in 2017. They recommend it as an option for the treatment of severe eosinophilic asthma that is not adequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug in individuals who have an eosinophil count of 400 cells/µL or greater and have had 3 or more severe exacerbations in the past year. They recommend assessing response annually. And adequate response is a reduction in exacerbations and or a reduction in oral corticosteroid use while maintaining control.

The NICE final assessment for benralizumab is expected in December 2018. The preliminary recommendation is that benralizumab is not recommended for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy that includes high dose ICS and LABAs.

CADTH Canadian Agency for Drugs and Technologies in Health

CADTH conducted a review of omalizumab treatment for adults and children with allergic asthma in 2015. They published a summary with a critical appraisal. They concluded that omalizumab decreases the risk of asthma exacerbations in patients with moderate to severe allergic asthma inadequately controlled by standard therapies. They acknowledged that one evidence-based guideline recommended its use for the treatment of individuals aged 6 and older who had severe persistent confirmed allergic IgE mediated asthma as an add on to optimized standard therapy for those who need frequent treatment with oral corticosteroids.

CADTH evaluated mepolizumab in 2015. They recommended it to be used as add-on maintenance treatment of adults with severe eosinophilic asthma who are inadequately controlled with high dose inhaled corticosteroids and one or more additional controllers and have a blood eosinophil count of 150 cells/microL or greater at initiation or ≥300 cells/microL in the past 12 months. Eligible patients must have experienced two or more clinically significant exacerbations in the past 12 months and show reversibility (at least 12% and 200 mL) on pulmonary function tests OR be on daily oral corticosteroids.

CADTH evaluated reslizumab in 2016. They recommended that reslizumab be used as add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with a medium to high dose inhaled corticosteroid and an additional controller, and who have a blood eosinophil count of ≥400 cells/microL, if they have had one or more clinically significant asthma exacerbations in the past 12 months and have an Asthma Control Questionnaire

7 score ≥1.5 points and show some reversibility (at least 12% and 200 ml) on pulmonary function tests.

CADTH evaluated benralizumab in 2018. They recommended that benralizumab be reimbursed as an add on maintenance treatment for adult patients with severe eosinophilic asthma. Patients eligible for treatment include those inadequately controlled with high dose inhaled corticosteroids and one or more additional asthma controllers if either 1) the blood eosinophil count is ≥300 mcg/L and patient has experienced two or more clinically significant asthma exacerbations in the past 12 months or 2) eosinophil count of ≥150 mcg/L and treated chronically with oral corticosteroids.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Head-to-Head Studies					
Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma (PREDICTUMAB) **NCT03476109** **Sponsor: Cliniques universitaires Saint-Luc- Université Catholique de Louvain**	Phase 4 Factorial assignment Single Blind (outcome assessor) RCT Estimated enrollment: 100	•Omalizumab (non-responders to be switched to mepolizumab) •Mepolizumab (non-responders to be switched to omalizumab)	Inclusion Criteria: •Age ≥18 years •Documented physician-diagnosed asthma •Severe disease and eligible for omalizumab and mepolizumab who have not yet received these therapies Exclusion Criteria: •History of evidence of drug/substance abuse that would pose a risk to patient safety, interfere with the conduct of study, have an impact on the study results, or affect the patient's ability to participate in the study •Treatment with an investigational therapy with 6 months or 5 drug half-lives prior to enrolment •Sensitivity to any of the active substances or their excipients to be administered during the study.	Primary Outcomes: •Asthma symptoms (Asthma Control Test) •Lung function (FEV1) •Number of severe exacerbations Secondary Outcomes: •Predictive factors of therapeutic response	December 31, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Omalizumab					
Preventing Asthma in High Risk Kids (PARK) **NCT02570984** **Sponsor: Wanda Phipatanakul**	Phase 2 Parallel assignment Quadruple masked RCT Estimated enrollment: 250	•Omalizumab •Placebo	Inclusion Criteria: •Age 24-47 months •Positive allergy to aeroallergen •2-4 wheezing episodes in past year •First degree relative with history or current diagnosis of asthma or allergy Exclusion Criteria: •>4 episodes of wheezing in the past year •Inhaled steroids with/without LABAs for respiratory symptoms within 4 weeks prior to screening •Systemic corticosteroids or hospitalization for respiratory symptoms within 4 weeks prior to screening •≥3 courses of systemic corticosteroids for wheezing in the last year •≥4 days of wheezing, tightness in the chest or cough in past 2 weeks that limit activity •≥4 days of albuterol for symptoms in past 2 weeks •Prematurity •≥5 days of oxygen during neonatal period •History of intubation or mechanical ventilation for respiratory illness •Prior aeroallergen immunotherapy, biologics, IVIG, systemic immunosuppressant •History of hypoxic seizures during wheezing episode •IgE outside omalizumab dosing range	Primary Outcomes: •Active asthma diagnosis •Asthma severity Secondary Outcomes: •Number of positive new allergic sensitization •Decrease in number of wheezing episodes	September 2023

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Mepolizumab					
A Safety and Efficacy Study of Mepolizumab in Subjects with Severe Asthma **NCT03562195** **Sponsor: GlaxoSmithKline**	Phase 3 Parallel assignment Double blind RCT Estimated enrollment: 300	•Mepolizumab (100mg) + Salbutamol •Placebo + Salbutamol	Inclusion Criteria: •Age ≥12 years •Weight ≥40kgs •Persistent airflow obstruction •Eosinophilic asthma •Regular high dose ICS in prior 12 months •Current treatment with additional controller medication for ≥3 months •History of ≥2 exacerbations requiring systemic corticosteroid in 12 months prior to Visit 1 Exclusion Criteria: •Current or former smoker •Bronchial thermoplasty and radiotherapy •Clinically significant cardiovascular disease, respiratory, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematological, or any other system abnormalities or conditions uncontrolled with standard treatment •Alcohol misuse or substance abuse •QT interval corrected by Fridericia's formula (QTc[F]) >450 milliseconds (msec) or QTc(F) >480 msec for subjects with Bundle Branch Block at Visit 1 •Other conditions that could lead to elevated eosinophils •Previous mepolizumab study participation, previous omalizumab or other monoclonal antibodies	Primary Outcome: •Clinically significant exacerbations Secondary Outcomes: •Time to first clinically significant exacerbation •Mean change from baseline in St. George's Respiratory Questionnaire •Exacerbations requiring hospitalization or ED visits •Exacerbations requiring hospitalization •Mean change from baseline in clinic prebronchodilator FEV1 •Number of subjects with adverse events including systemic and injection site reactions •Number of subjects with abnormal hematology, clinical chemistry, blood pressure, pulse rate, ECG parameters •Number of subjects with anti-mepolizumab antibody positive results •Change from baseline in blood eosinophil ratio	March 31, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Benralizumab					
Efficacy and Safety Study of Benralizumab in Patients with Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA (MIRACLE) **NCT03186209** **Sponsor: AstraZeneca**	Phase 3 Parallel assignment Triple blind RCT Estimated enrollment: 666	•Benralizumab •Placebo	Inclusion Criteria: •Age 12-75 years •Physician-diagnosed asthma requiring treatment with medium-to-high dose ICS and a LABA for ≥6 months prior to Visit 1 •Additional maintenance controller medications •≥2 documented asthma exacerbations in previous 12 months with ≥1 exacerbation occurring during treatment of medium-to-high dose ICS-LABA •Post-bronchodilator (post-BD) reversibility in FEV1 of >12% and >200 mL in FEV1 within 12 months prior to Visit 1 •>2 days with symptoms score >1 or SABA use >2 days or ≥1 nocturnal awakening due to asthma Exclusion Criteria: •Clinically important pulmonary disease other than asthma or any systemic disease associated with elevated peripheral eosinophil counts •Any disorder or abnormal findings that could influence safety, participation, or study findings •Acute upper or lower respiratory infections requiring antibiotics or antiviral medication •Current or former smokers	Primary Outcome: •Annual asthma exacerbation rate Secondary Outcomes: Change from baseline: •Pre-bronchodilator FEV1 • Asthma Symptom Score • ACQ6 •SGRQ •Time to First Asthma Exacerbation •Patients with ≥1 asthma exacerbation •Annual asthma exacerbation rate associated with an ED/urgent care visit or hospitalization •Participants that utilized Health Care resources •Mean PK concentrations •Immunogenicity •Blood eosinophil levels •Change in asthma rescue medication •Morning and evening PEF •Night awakening due to asthma	February 26, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of the Safety and Effectiveness of Benralizumab to Treat Patients with Severe Uncontrolled Asthma (ANDHI) **NCT03170271** **Sponsor: AstraZeneca**	Phase 3 Parallel assignment Double blind RCT Estimated enrollment: 630	•Benralizumab •Placebo	Inclusion Criteria: •Age 18-75 years •High daily doses of ICS plus ≥1 other asthma controller for ≥3 months prior to Visit 1 •≥2 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids in 12 months prior to Visit 1 •ACQ6 ≥1.5 •Pre-bronchodilator FEV1 <80% predicted at Visit 2 •Excessive variability in lung function •Peripheral blood eosinophil count of 300 cells/µ or 150-300 cells/µ if using maintenance OCS, history of nasal polyposis, age of asthma onset ≥18 years, ≥3 exacerbations in previous 12 months, or pre-bronchodilator forced vital capacity <65% of predicted Exclusion Criteria: •Other clinically important pulmonary disease •Acute upper or lower respiratory infections within 30 days •Helminth parasitic infection within 24 weeks •Drug or alcohol abuse within 12 months •Smokers or former smokers •History of known immunodeficiency disorder •Previous benralizumab, investigational medication (within 5 half-lives), immunoglobulin or blood products (within 30 days), live attenuated vaccines (within 30 days)	Primary Outcome: •Annualized rate of asthma exacerbations Secondary Outcome: •Change from baseline in SGRQ	August 13, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Dupilumab					
Evaluation of Dupilumab in Children with Uncontrolled Asthma (VOYAGE) **NCT02948959** Sponsor(s): Sanofi, Regeneron Pharmaceuticals	Phase 3 Parallel assignment Triple masked RCT Estimated enrollment: 294	•Dupilumab •Placebo •Asthma controller therapies (including prednisone/ prednisolone) •Asthma reliever therapies	Inclusion criteria •Age 6 to <12 years of age with a physician diagnosis of persistent asthma for ≥12 months prior to Screening, based on clinical history and examination, pulmonary function parameters according to GINA 2015 Guidelines and the following criteria: •Existing background therapy of medium-dose ICS with second controller medication or high-dose ICS with or without second controller, for at least 3 months •Pre-bronchodilator FEV1≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio <0.85 at Screening and Baseline visits. •Reversibility of at least 10% in FEV1 after the administration of albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication •Treatment with a systemic corticosteroid for worsening asthma at least once in previous year, or hospitalization or emergency room visit for worsening asthma in previous year •Evidence of uncontrolled asthma	Primary Outcome: •Annualized rate of severe exacerbation events Secondary Outcomes: Change from baseline in: •Pre-bronchodilator % predicted FEV1 • Other lung function measurements •Morning and evening asthma symptom scores •Time to first severe exacerbation event •Time to first loss of asthma control event •Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication •Use of reliever medication	July 22, 2021

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. 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 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 D3)[60] 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.*

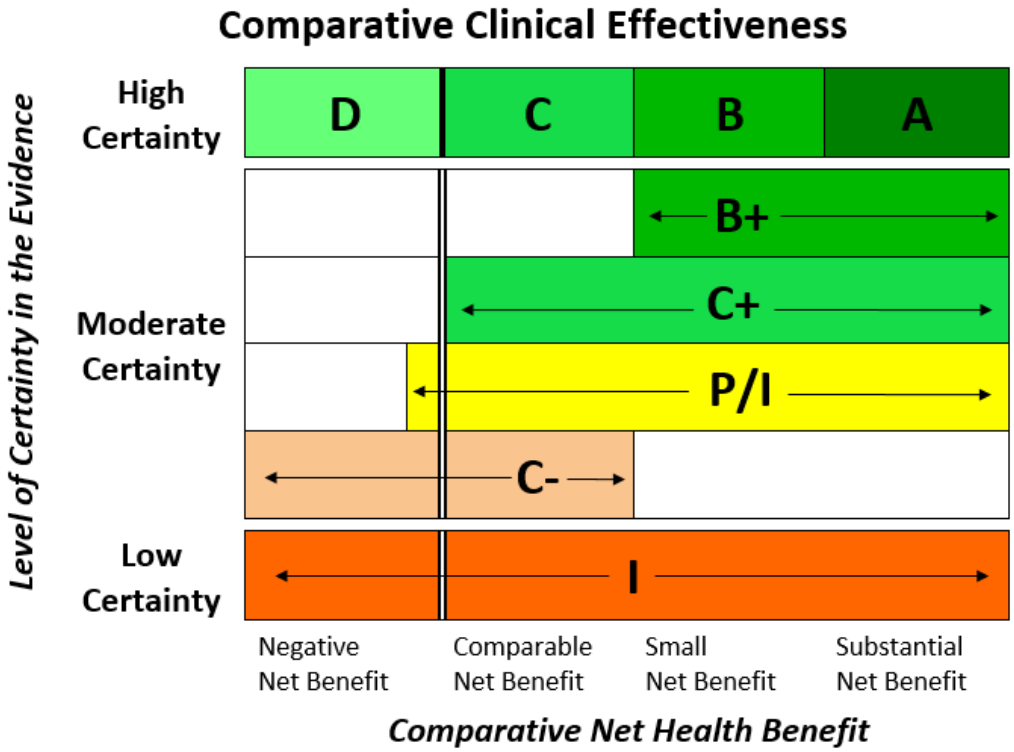
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) 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.[113]

Figure D1. 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 or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Overview of Studies

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Omalizumab													
Allergic asthma / asthma with elevated Ige													
Vignola 2004[114] **SOLAR (N=405)**		28	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	38.4	55	20	78	18	NR	0	N/A	2.1
Humbert 2005[65] **INNOVATE (n=419)**	3	28	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	43.3	43	23	61	27	3.9	22	N/A	2.1
Busse 2011[67] **ICATA (n=419)**	3	60	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	10.8	42	7.3	92	NR	NR	0	N/A	NR
Hanania 2011[115] (n=850)	3	48	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	44.5	66	23.7	64.9	NR	NR	17	N/A	2

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Bardelas 2012[116] (n=271)	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	41.5	66	NR	76	NR	NR	0	N/A	NR
Busse 2013[19] (n=328)	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	36	69	NR	86%	NR	NR	NR	N/A	NR
Li 2016[117] **China omalizumab (n=616)**	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	46.5	54	14.7	62.50%	27%	NR	NR	N/A	NR
Mepolizumab													
Severe eosinophilic asthma													
Pavord 2012[66] **DREAM (n=616)**	3	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

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Ortega 2014[87] **MENSA (n=576)**	3	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
Chupp 2017[89] **MUSCA (n=551)**	3	24	Mepolizumab 100 mg SC q 4 weeks Placebo	Severe eosinophilic asthma	51	59	19.5	55	21	2.2	24	325	2.8
OCS-dependent eosinophilic asthma													
Bel 2014[70] **SIRIUS (n=135)**	3	24	Mepolizumab 100 mg SC q4 weeks Placebo	Chronic OCS use	50	55	19	59	26	2.2	100	240	3.1
Reslizumab													
Severe eosinophilic asthma													
Castro 2015[88] (n=953)	3	64	Reslizumab 3.0 mg/kg q 4 weeks Placebo	Poorly controlled eosinophilic asthma	48	61	14	66	18	2.7	17	655	2
Benralizumab													
Bleecker 2016[62] **SIROCCO (n=1205)**	3	48	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Asthma on medium or high dose ICS and at least 2 exacerbations	48	66	14	57	20	2.87	NR	370	3.1

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Fitzgerald 2016[63] **CALIMA (n=1306)**	3	56	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Poorly controlled eosinophilic asthma	49	62	16	58	20	2.7	NR	380	2.7
OCS-dependent severe eosinophilic asthma													
Nair 2017[71] **ZONDA (n=220)**	3	28	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Eosinophilic asthma requiring OCS for control	51.4	64	13.4	60.5	19.5	2.6	NR	486	2.8
Dupilumab													
Moderate to severe uncontrolled asthma													
Wenzel 2016[118] (n=769)	2b	24	Dupilumab 200 or 300 mg every 2 or 4 weeks Placebo	Uncontrolled persistent asthma on ICS	49	63	22	61	NR	2.74	0	347	2.17
Castro 2018[16] **LIBERTY ASTHMA QUEST (n=1902)**	3	52	Dupilumab 200 mg or 300 mg SQ every two weeks Placebo	Moderate to severe uncontrolled asthma	47.9	63	NR	1.78	26	2.76	0	360	2.09
OCS-dependent severe asthma													

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Rabe 2018[17] LIBERTY ASTHMA VENTURE (n=210)	3	24	Dupilumab 300 mg SQ ever 2 weeks Placebo	Chronic OCS use	51.3	60	NR	52	18	2.5	100	347	2.09

ACQ: Asthma Control Questionnaire; FEV1: forced expiratory volume in one second, FU: follow-up, N/A: not applicable, NR: not reported, OCS; oral corticosteroids

Table D2. Key Inclusion Criteria

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
Omalizumab												
Allergic asthma/asthma with elevated IgE												
Vignola 2004[114] SOLAR	405	12-75	Moderate to severe	N/A	≥12%	≥2	High dose ICS	Excluded if OCS	N/A	N/A	≥30 to ≤1300 IU/ml	-
Humbert 2005[65] INNOVATE	419	12-75	Severe	≥40 to ≤80% predicted	≥12%	≥2	High dose ICS and another controller	Maintenance permitted if at least one exacerbation occurred on OCS	NR	NR	>30 to <700 IU/ml	-
Busse 2011[67] ICATA	419	6-20	Severe	N/A	N/A	≥1	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-
Hanania 2011[115]	850	12-75	Severe	≥40 to ≤80% predicted	NR	≥1	High dose ICS and another controller	Maintenance permitted	NR	NR	>30 to <700 IU/ml	-
Bardelas 2012[116]	271	≥12	Severe	≤80% predicted	NR	dx ≥12m	Medium dose ICS and another controller	No	N/A	N/A	>30 to <700 IU/ml	-

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
Busse 2013[19]	328	12-75	Severe	>80% predicted	N/A	≥1	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-
Li 2016[117]	616	18-75	Moderate to severe	≥40 to ≤80% predicted	≥12%	≥2	Medium dose ICS and another controller	No	N/A	N/A	NR	-
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	616	12-74	Severe		Improvement >12% with inhaled salmeterol or variability of more than 20% between clinic visits	≥2	≥880 mcg fluticasone with or without OCS	No	>300	3% or more	NR	NR
Ortega 2014[87] MENSA	576	12-82	Severe	<80% predicted for adults or <90% predicted for adolescents	>12%	≥2	≥880 mcg fluticasone and another controller	No	>150 at screening or >300 in previous year	NR	NR	NR
Chupp 2017[89]	551	≥12	Severe	<80% predicted for adults or	NR	≥2	High does ICS and	If on OCS, exacerbations	>150 at screening or >300 in	NR	NR	NR

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
MUSCA				<90% predicted for adolescents			another controller	requiring doubling	previous year			
OCS-dependent severe eosinophilic asthma												
Bel 2014[70] SIRIUS	135	≥12	Severe	NR	NR	NR	≥880 mcg fluticasone and another controller	≥6 months OCS; ≥40 mcg for age 12-17	>300 during 12 months before or <150 during optimi-zation	NR	NR	NR
Reslizumab												
Castro 2015[88]	953	12-75	Moderate to severe	NR	≥12%	≥1	≥440 mcg fluticasone with or without another controller including OCS	Allowed	≥400	NR	NR	≥1.5
Benralizumab												
Bleecker 2016[62] SIROCCO	1205	12-75	Severe	<80% predicted for adults or	≥12%	≥2	high dose ICS; med	No	NR	NR	NR	>1.5

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
				<90% predicted for adolescents			or high for age 12-17					
Fitzgerald 2016[63] CALIMA	1306	12-75	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	≥2	Med. (≥250 mcg) to high dose ICS (≥500 mcg) fluticasone with another controller	No	>300	NR	NR	NR
OCS-dependent severe eosinophilic asthma												
Nair 2017[71] ZONDA	220	Adults	OCS for at least 6 months	NR	NR	NR	NR	NR	≥150	NR	NR	NR
Dupilumab												
Wenzel 2016[118]	769	≥18	Moderate to severe	≥40 to ≤80% predicted	≥12%	≥1	≥500 mcg fluticasone and at least one other controller	NR	NR	NR	NR	≥1.5
Castro 2018[16] LIBERTY ASTHMA QUEST	1902	≥12	Moderate to severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	≥1	≥500 mcg fluticasone and up to two other controllers	NR	No minimum	No minimum	NR	NR

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
OCS-dependent severe asthma												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	210	≥12	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	NR	≥500 mcg fluticasone ad up to two other controllers	On OCS	No minimum	No min-imum	N/A	NR

ACQ: Asthma Control Questionnaire, ICS: inhaled corticosteroids, FEV1: forced expiratory volume in one second, N/A: not applicable, NR: not reported, OCS: oral corticosteroids

Table D3. Study Quality Metrics

Reference & Study Name	Adequate randomization	Allocation concealment	Patient 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
Omalizumab												
Vignola 2004[114] SOLAR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Humbert 2005[65] INNOVATE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2011[67] ICATA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Hanania 2011[115]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Bardelas 2012[116]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2013[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Li 2016[117] Chinese Omalizumab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	Yes	Yes	Yes	Yes	Yes	16% withdrew	Yes	Yes	No	Yes	Yes	Good
Ortega 2014[87] MENSA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

Reference & Study Name	Adequate randomization	Allocation concealment	Patient 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
Chupp 2017[89] MUSCA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Bel 2014[70] SIRIUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Reslizumab												
Severe eosinophilic asthma												
Castro 2015[88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Benralizumab												
Bleecker 2016[62] SIROCCO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Fitzgerald 2016[63] CALIMA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Nair 2017[71] ZONDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Dupilumab												
Moderate to severe uncontrolled asthma												
Wenzel 2016[118]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Castro 2018[16] LIBERTY ASTHMA QUEST	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

Reference & Study Name	Adequate randomization	Allocation concealment	Patient 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
OCS-dependent												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

OCS: oral corticosteroids

Table D4. Key Outcomes: Exacerbations and Changes in FEV1

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
Omalizumab							
Asthma with elevated IgE							
Vignola 2004[114] SOLAR	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR
	Placebo	196	NR	NR	NR	NR	NR
Humbert 2005[65] INNOVATE	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	0.68	0.24	0.06	190	
	Placebo	210	0.91	0.43	0.12	96	
	Rate Ratio		0.738 (0.552-0.998)	0.56 (0.33-0.97)	0.54 (0.25-1.1.7)	NR	NR
Busse 2011[67] ICATA	Omalizumab 0.016 mg/kg per IU/ml of IGE	208	NR	NR	NR	NR	NR
	Placebo	211	NR	NR	NR	NR	NR
Hanania 2011[115]	Omalizumab 0.016 mg/kg per IU/ml of IGE	427	0.66	NR	NR	NR	NR
	Placebo	423	0.88	NR	NR	NR	NR
	Rate ratio	NR	0.75 (0.61-0.92)	NR	NR	NR	NR
Bardelas 2012[116]	Omalizumab 0.016 mg/kg per IU/ml of IGE	136	NR	NR	NR	NR	NR
	Placebo	135	NR	NR	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
Busse 2013[19]	Omalizumab 0.016 mg/kg per IU/ml of IGE	51	0.25	NR	NR	NR	NR
	Placebo	40	0.59	NR	NR	NR	NR
	Rate ratio		0.41 (0.20-0.82)	NR	NR	NR	NR
Li 2016[117] China Omalizumab	Omalizumab 0.016 mg/kg per IU/ml of IGE	310	NR	NR	NR	NR	NR
	Placebo	299	NR	NR	NR	NR	NR
	Rate ratio	NR	0.61	NR	NR	NR	NR
Mepolizumab							
Severe eosinophilic asthma							
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	1.24	0.17	0.1	NR	NR
	Mepolizumab 250 mg IV	152	1.46	0.25	0.1	NR	NR
	Mepolizumab 750 mg IV	156	1.15	0.22	0.07	NR	NR
	Placebo	155	2.4	0.43	0.2	NR	NR
Ortega 2014[87] MENSA	Mepolizumab 75 mg IV	191	0.93	0.14	0.06	186	176
	Mepolizumab 100 mg SC	194	0.83	0.08	0.03	183	167
	Placebo	191	1.74	0.2	0.1	68	30
	Difference SC vs. Placebo		53% (36%-65%)	61% (17%-82%)	69% (9%-89%)	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
Chupp 2017[89] MUSCA	Mepolizumab 100 SQ	274	0.51	0.03	0.02	176	NR
	Placebo	277	1.21	0.1	0.07	56	NR
	Difference	NR	0.42* (0.31-0.56)	0.32 (0.12-0.90)	0.31 (0.0-1.24)	120 (47-192)	NR
OCS-dependent							
Bel 2014[70] SIRIUS	Mepolizumab 100 mg SC	69	1.44	NR	0	NR	NR
	Placebo	66	2.12	NR	NR	NR	NR
	Rate ratio	NR	0.68 (0.47-0.99)	NR	NR	NR	NR
Reslizumab							
Poorly controlled eosinophilic asthma							
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	NR	0.077	NR	220	NR
	Placebo	476	NR	0.12	NR	120	NR
	Rate Ratio	NR	NR	0.66 (0.38-1.16)	NR	0.11 (0.067-0.15)	NR
Benralizumab							
Bleecker 2016[62] SIROCCO	Benralizumab 30 mg q 4 weeks	399 (275)	0.73	NR	NR	345	NR
	Benralizumab 30 mg q 8 weeks	398 (267)	0.65	NR	NR	398	NR
	Placebo	407 (261)	1.33	NR	NR	239	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
	Rate Ratio for 30 q 4	NR	0.55 (0.42-0.71)	NR	NR	NR	NR
	Rate Ratio for 30 q 8	NR	0.49 (0.37-0.64)	NR	NR	NR	NR
Fitzgerald 2016[63] CALIMA	Benralizumab 30 mg q 4 weeks	425 (241)	0.6	NR	NR	340	NR
	Benralizumab 30 mg q 8 weeks	441 (239)	0.66	NR	NR	330	NR
	Placebo	440 (248)	0.93	NR	NR	215	NR
	Rate Ratio for 30 q 4	NR	0.64 (0.49-0.85)	0.93 (0.48-1.92)	NR	NR	NR
	Rate Ratio for 30 q 8	NR	0.72 (0.54-0.95	1.23 (0.64-2.35)	NR	NR	NR
OCS-dependent							
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	0.83	0.14	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	73	0.54	0.02	NR	NR	NR
	Placebo	75	1.83	0.32	NR	NR	NR
	Rate Ratio for 30 q 4	NR	0.45 (0.27-0.76)	0.44 (0.13-1.49)	Difference q 4	256	NR
	Rate Ratio for 30 q 8	NR	0.30 (0.17-0.53)	0.07 (0.01-0.63)	Difference q 8	222	NR
Dupilumab							

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
Moderate to severe uncontrolled asthma							
Wenzel 2016[118]	Dupilumab 200 mg SC q 2 weeks	154	0.42	NR	NR	0.26	NR
	Dupilumab 20 mg q 4 weeks	157	0.599	NR	NR	0.23	NR
	Dupilumab 300 mg q 2 weeks	150	0.269	NR	NR	0.26	NR
	Dupilumab 300 mg q 4 weeks	157	0.265	NR	NR	0.29	NR
	Placebo	158	0.897	NR	NR	0.28	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg SC q 2 weeks	621	0.46 (0.39-0.53)	NR	NR	0.32	NR
	Placebo 200 mg	317	0.87 (0.72-1.05)	NR	NR	0.18	NR
	Dupilumab 300 mg SC q 2 weeks	633	0.52 (0.45-0.61)	NR	NR	0.34	NR
	Placebo 300 mg	321	0.97 (0.81-1.16)	NR	NR	0.21	NR
	Rate Ratio 200 mg vs. Placebo	NR	0.52 (0.41 to 0.66)	NR	NR	NR	NR
	Rate Ratio 300 mg vs. Placebo	NR	0.54 (0.43 to 0.68)	NR	NR	NR	NR
Glucocorticoid dependent Severe asthma							

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	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
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	0.7	NR	NR	0.21	NR
	Placebo	107	1.6	NR	NR	0.01	NR
	Rate Ratio vs Placebo	NR	0.59	NR	NR	NR	NR

ER: emergency room, FEV1: forced expiratory volume in one second, IV: intravenous, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, SC: subcutaneous

Table D5. Key Outcomes: Quality of Life and Reductions in OCS Dose

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
Omalizumab								
Asthma with elevated IgE								
Vignola 2004[114] SOLAR	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR	NR
	Placebo	196	NR	NR	NR	NR	NR	NR
Humbert 2005[65] INNOVATE	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR	NR
	Placebo	210	NR	NR	NR	NR	NR	NR
	Rate Ratio	NR	NR	NR	NR	NR	NR	NR
Busse 2011[67] ICATA	Omalizumab 0.016 mg/kg per IU/ml of IGE	208	NR	NR	NR	N/A	N/A	N/A
	Placebo	211	NR	NR	NR	NR	NR	NR
Hanania 2011[115]	Omalizumab 0.016 mg/kg per IU/ml of IGE	NR	NR	0.29	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR
Bardelas 2012[116]	Omalizumab 0.016 mg/kg per IU/ml of IGE	136	NR	NR	NR	N/A	N/A	N/A
	Placebo	135	NR	NR	NR	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
Busse 2013[19]	Omalizumab 0.016 mg/kg per IU/ml of IGE	51	NR	NR	NR	NR	NR	NR
	Placebo	40	NR	NR	NR	NR	NR	NR
Li 2016[117] China Omalizumab	Omalizumab 0.016 mg/kg per IU/ml of IGE	310	NR	NR	NR	N/A	N/A	N/A
	Placebo	299	NR	NR	NR	NR	NR	NR
Mepolizumab								
Severe eosinophilic asthma								
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	-0.75	NR	NR	NR	NR	NR
	Mepolizumab 250 mg IV	152	-0.87	NR	NR	NR	NR	NR
	Mepolizumab 750 mg IV	156	-0.8	NR	NR	NR	NR	NR
	Placebo	155	-0.59	NR	NR	NR	NR	NR
Ortega 2014[87] MENSA	Mepolizumab 75 mg IV	191	-0.92	NR	-15.4	NR	NR	NR
	Mepolizumab 100 mg SC	194	-0.94	NR	-16	NR	NR	NR
	Placebo	191	-0.5	NR	-9	NR	NR	NR
	Difference SC vs. Placebo	NR	-0.44 (-0.63 to -0.25)	NR	-7 (-10.2 to -3.8)	NR	NR	NR
Chupp 2017[89] MUSCA	Mepolizumab 100 SQ	274	-0.8	NR	-15.6	NR	NR	NR
	Placebo	277	-0.4	NR	-7.9	NR	NR	NR
	Difference	NR	-0.4	NR	-7.7	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
			(-0.6 to -0.2)					
OCS-dependent								
Bel 2014[70] SIRIUS	Mepolizumab 100 mg SC	69	NR	NR	NR	23%	54%	36%
	Placebo	66	NR	NR	NR	11%	33%	56%
	Difference	NR	-0.52 (-0.87 to -0.17)	NR	-5.8 (-10.1 to -1.0)	NR	NR	NR
Reslizumab								
Poorly controlled eosinophilic asthma								
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	-1.02	NR	NR	NR	NR	NR
	Placebo	476	-0.77	NR	NR	NR	NR	NR
	Rate Ratio	NR	-0.25	NR	NR	NR	NR	NR
Benralizumab								
Bleecker 2016[62] SIROCCO	Benralizumab 30 mg q 4 weeks	399 (275)	-1.12	NR	NR	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	398 (267)	-1.3	NR	NR	NR	NR	NR
	Placebo	407 (261)	-1.04	NR	NR	NR	NR	NR
Fitzgerald 2016[63] CALIMA	Benralizumab 30 mg q 4 weeks	425 (241)	-1.4	NR	NR	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	441 (239)	NR	NR	NR	NR	NR	NR
	Placebo	440 (248)	-1.16	NR	NR	NR	NR	NR
OCS-dependent								
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	NR	NR	NR	33%	67%	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
	Benralizumab 30 mg q 8 weeks	73	NR	NR	NR	37%	66%	NR
	Placebo	75	NR	NR	NR	12%	37%	NR
Dupilumab								
Moderate to severe uncontrolled asthma								
Wenzel 2016[118]	Dupilumab 200 mg SC q 2 weeks	154	-1.32	NR	NR	NR	NR	NR
	Dupilumab 20 mg q 4 weeks	157	-1.34	NR	NR	NR	NR	NR
	Dupilumab 300 mg q 2 weeks	150	-1.49	NR	NR	NR	NR	NR
	Dupilumab 300 mg q 4 weeks	157	-1.45	NR	NR	NR	NR	NR
	Placebo	158	-1.14	NR	NR	NR	NR	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg SC q 2 weeks	631	-1.44	128	NR	NR	NR	NR
	Placebo 200 mg	317	-1.10	0.99	NR	NR	NR	NR
	Dupilumab 300 mg SC q 2 weeks	633	-1.40	1.29	NR	NR	NR	NR
	Placebo 300 mg	321	-1.21	1.03	NR	NR	NR	NR
Glucocorticoid dependent Severe asthma								
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	NR	NR	NR	NR	80%	NR
	Placebo	107	NR	NR	NR	NR	50%	NR

ACQ: Asthma Control Questionnaire, ER: emergency Room, FEV1: forced expiratory volume in one second, IV: intravenous, N/A: not applicable, NR: not reported, OCS: oral corticosteroid, SGRQ: St. George's Respiratory Questionnaire, SC: subcutaneous

Table D6. Harms

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
Omalizumab												
Vignola 2004[114]	Omalizumab	209	78%	6.2%	0	NR	0	NR	7.70%	NR	NR	NR
	Placebo	196	69%	9.2%	0	NR	0	NR	4.60%	NR	NR	NR
Humbert 2005[65]	Omalizumab	419	72%	12%	0	12%	NR	NR	5%	7%	5%	6%
	Placebo	NR	76%	16%	0	9%	NR	NR	5%	9%	6%	8%
Busse 2011[67]	Omalizumab	NR	39%	6%	0	NR	NR	NR	4%	NR	NR	NR
	Placebo	NR	47%	14%	0	NR	NR	NR	3%	NR	NR	NR
Hanania 2011[115]	Omalizumab	NR	80	NR	0	NR	3.7	1.6	1.2	NR	NR	NR
	Placebo	NR	80	NR	1	NR	2.4	2.9	3.1	NR	NR	NR
Bardelas 2012[116]	Omalizumab	136	66	NR	NR	8%	NR	NR	NR	5%	11%	10%
	Placebo	135	69	NR	NR	3%	NR	NR	NR	7%	13%	7%
Busse 2013[19]	Omalizumab	157	59	2.50%	0	NR	2%	1.30%	1.30%	NR	9.60%	7.00%
	Placebo	171	63	3.50%	0	NR	1%	2.30%	0.60%	NR	9.90%	9.40%
Li 2016[117]	Omalizumab	310	39%	1.90%	0	NR	NR	NR	NR	1.00%	12.90%	NR
	Placebo	299	40%	3%	0	NR	NR	NR	NR	1.30%	13%	NR
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	NR	13%	0 (0%)	NR	3%	NR	NR	NR	NR	NR
	Mepolizumab 250 mg IV	152	NR	16%	2 (1%)	NR	5%	NR	NR	NR	NR	NR
	Mepolizumab 750 mg IV	156	NR	12%	1 (1%)	NR	6%	NR	NR	NR	NR	NR
	Placebo	155	NR	16%	0 (0%)	NR	4%	NR	NR	NR	NR	NR
Ortega 2014[87]	Mepolizumab 75 mg IV	191	84%	7%	0 (0%)	17%	0%	NR	3%	24%	12%	6%

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
MENSA	Mepolizumab 100 mg SC	194	78%	8%	0 (0%)	20%	1%	NR	9%	20%	12%	9%
	Placebo	191	83%	14%	1 (1%)	16%	2%	NR	3%	17%	14%	9%
Chupp 2017[89] **MUSCA**	Mepolizumab 100 SQ	274	70%	5%	0%	11%	1%	NR	3%	16%	6%	NR
	Placebo	277	74%	8%	0%	9%	1%	NR	2%	21%	5%	NR
OCS-dependent												
Bel 2014[70] **SIRIUS**	Mepolizumab 100 mg SC	69	83%	1%	0 (0%)	30%	5%	NR	6%	20%	4%	10%
	Placebo	66	92%	18%	1 (2%)	18%	4%	NR	3%	21%	8%	9%
Reslizumab 3 mg/kg IV												
Severe eosinophilic asthma												
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	78%	9%	0	NR	3%	NR	NR	11%	10%	7%
	Placebo	476	86%	12%	0	NR	4%	NR	NR	11%	10%	8%
Benralizumab												
Bleecker 2016[62]	Benralizumab 30 mg q 4 weeks	293	73%	12%	<1%	NR	2%	3%	4%	7%	11%	4%
	Benralizumab 30 mg q 8 weeks	281	71%	13%	<1%	NR	2%	3%	2%	9%	8%	6%
	Placebo	311	76%	14%	1%	NR	<1%	3%	2%	5%	9%	7%
Fitzgerald 2016[63] **CALIMA**	Benralizumab 30 mg q 4 weeks	425	74%	10%	<1%	12%	2%	3%	3%	8%	7%	5%
	Benralizumab 30 mg q 8 weeks	441	75%	9%	<1%	13%	2%	3%	3%	8%	8%	5%
	Placebo	440	78%	14%	0	8%	<1%	4%	2%	8%	9%	8%
OCS-dependent												

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	68%	10%	0%	NR	0%	1%	3%	7%	6%	7%
	Benralizumab 30 mg q 8 weeks	73	75%	10%	3%	NR	4%	3%	0%	8%	7%	5%
	Placebo	75	83%	19%	0%	NR	3%	1%	3%	5%	7%	11%
Dupilumab												
Wenzel 2016[118]	Dupilumab 200 mg every 4 weeks	154	75%	4%	0	NR	5%	NR	9%	6%	15%	NR
	Dupilumab 300 mg every 4 weeks	157	83%	10%	1%	NR	6%	NR	8%	12%	12%	NR
	Dupilumab 200 mg every 4 weeks	150	80%	8%	0	NR	4%	NR	14%	11%	15%	NR
	Dupilumab 300 mg every 4 weeks	157	78%	7%	0	NR	3%	NR	21%	11%	13%	NR
	Placebo	158	75%	6%	0	NR	3%	NR	8%	13%	18%	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg or 300 mg	1263	81%	8.20%	0.40%	NR	5%	NR	16.80%	6.80%	11.60%	4.90%
	Placebo	634	83%	8.40%	0.50%	NR	4.60%	NR	7.90%	8.00%	13.60%	8.80%
OCS-dependent												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	62%	9.00%	0.00%	NR	1.00%	NR	9.00%	NR	9.00%	7.00%
	Placebo	107	64%	6.00%	0.00%	NR	4.00%	NR	4.00%	NR	18.00%	4.00%

AE: adverse event, NR: not reported, SAE: severe adverse event, URI: upper respiratory infection

Network Meta-Analysis Supplemental Information

As described in the report, we conducted an exploratory network meta-analysis (NMA) of asthma exacerbations in the subgroup of patients with high baseline eosinophils (≥300 cells/L) and ≥2 exacerbations in the previous year. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]). The NMA was conducted in a Bayesian framework with random effects on the treatment parameter using the gemtc package in R.[119] The log exacerbation rates were analyzed using a normal likelihood and identity link. Inputs used for the analysis are reported in Appendix Table D7. Tabular results are presented for the treatment effects (rate ratio) of each intervention versus placebo along with 95% credible intervals (95% CrI) in Section 3 of the report.

Table D7. Network Meta-Analysis Inputs: Asthma Exacerbations in Patients with ≥300 eosinophils/µL and ≥2 Exacerbations in Previous Year

Study	Intervention(s)	Exacerbation Rate (95% CI)	Rate ratio vs. Placebo (95% CI)
Casale 2018[120]	Placebo	NR	0.33 (0.16, 0.64)
	Omalizumab	NR	
MENSA[87]	Placebo	2.04 (1.78, 2.30)	0.34 (0.21, 0.54)
	Mepolizumab	0.70 (0.31, 1.09)	
MUSCA[89]	Placebo	1.62 (1.37, 1.87)	0.38 (0.25, 0.58)
	Mepolizumab	0.62 (0.26, 0.98)	
Study 3082 &3083 (Castro 2015)[88]	Placebo	NR	0.34 (0.25, 0.47)
	Reslizumab	NR	
Study 3083 (Castro 2015)[88]	Placebo	NR	0.34 (0.25, 0.47)
	Reslizumab	NR	
CALIMA[63]	Placebo	0.93 (0.77, 1.12)	0.72 (0.54, 0.95)
	Benralizumab	0.66 (0.54, 0.82)	
SIROCCO[62]	Placebo	1.33 (1.12, 1.58)	0.49 (0.37, 0.64)
	Benralizumab	0.65 (0.53, 0.80)	
LIBERTY ASTHMA QUEST[16]	Placebo	NR	0.26 (0.19, 0.36)
	Dupilumab 200mg	NR	
	Placebo	NR	0.26 (0.19, 0.35)
	Dupilumab 300mg	NR	
Wenzel 2016[118]	Placebo	NR	0.26 (0.19, 0.36)
	Dupilumab 200mg	NR	
	Dupilumab 300mg	NR	0.26 (0.19, 0.35)

NR: not reported

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	Only included chronic oral steroid use changes
Medical costs	Paid by third-party payers	X	X	Included within unit cost estimates
	Paid by patients out-of-pocket	X	X	Included within unit cost estimates to the extent possible
	Future related medical costs	X	X	Included future asthma event and treatment costs
	Future unrelated medical costs	☐	☐	Non-asthma costs were not directly included
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Included in modified societal perspective
	Cost of unpaid lost productivity due to illness	NA	X	Included in modified societal perspective
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	

Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: Not applicable

Adapted from Sanders et al.[120]

Lifetime Annualized Clinical Outcomes

Tables E2 -E6 indicate the long-run clinical outcomes for all five biologic agents. This analysis investigated the average events per person year for oral corticosteroid burst, ED visit, hospitalization, and death (all cause). The exacerbation rate ratios drive these incremental findings.

Table E2. Long-Run Clinical Outcomes: Omalizumab

Omalizumab: Average Events per Person Year			
Average Events per Person Year	**Omalizumab**	**SoC**	**Incremental**
Steroid Burst	0.601	1.141	-0.540
ED Visit	0.026	0.063	-0.038
Hospitalization	0.010	0.063	-0.053
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E3. Long-Run Clinical Outcomes: Mepolizumab

Mepolizumab: Average Events per Person Year			
Average Events per Person Year	**Mepolizumab**	**SoC**	**Incremental**
Steroid Burst	0.521	1.141	-0.620
ED Visit	0.023	0.063	-0.040
Hospitalization	0.020	0.063	-0.043
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E4. Long-Run Clinical Outcomes: Reslizumab

Reslizumab: Average Events per Person Year			
Average Events per Person Year	**Reslizumab**	**SoC**	**Incremental**
Steroid Burst	0.497	1.141	-0.644
ED Visit	0.043	0.063	-0.020
Hospitalization	0.043	0.063	-0.020
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E5. Long-Run Clinical Outcomes: Benralizumab

Benralizumab: Average Events per Person Year			
Average Events per Person Year	**Benralizumab**	**SoC**	**Incremental**
Steroid Burst	0.680	1.141	-0.461
ED Visit	0.044	0.063	-0.020
Hospitalization	0.044	0.063	-0.020
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E6. Long-Run Clinical Outcomes: Dupilumab

Dupilumab: Average Events per Person Year			
Average Events per Person Year	**Dupilumab**	**SoC**	**Incremental**
Steroid Burst	0.463	1.141	-0.678
ED Visit	0.026	0.063	-0.038
Hospitalization	0.026	0.063	-0.038
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Sensitivity Analysis Results

Figure E1. Omalizumab Tornado Diagram

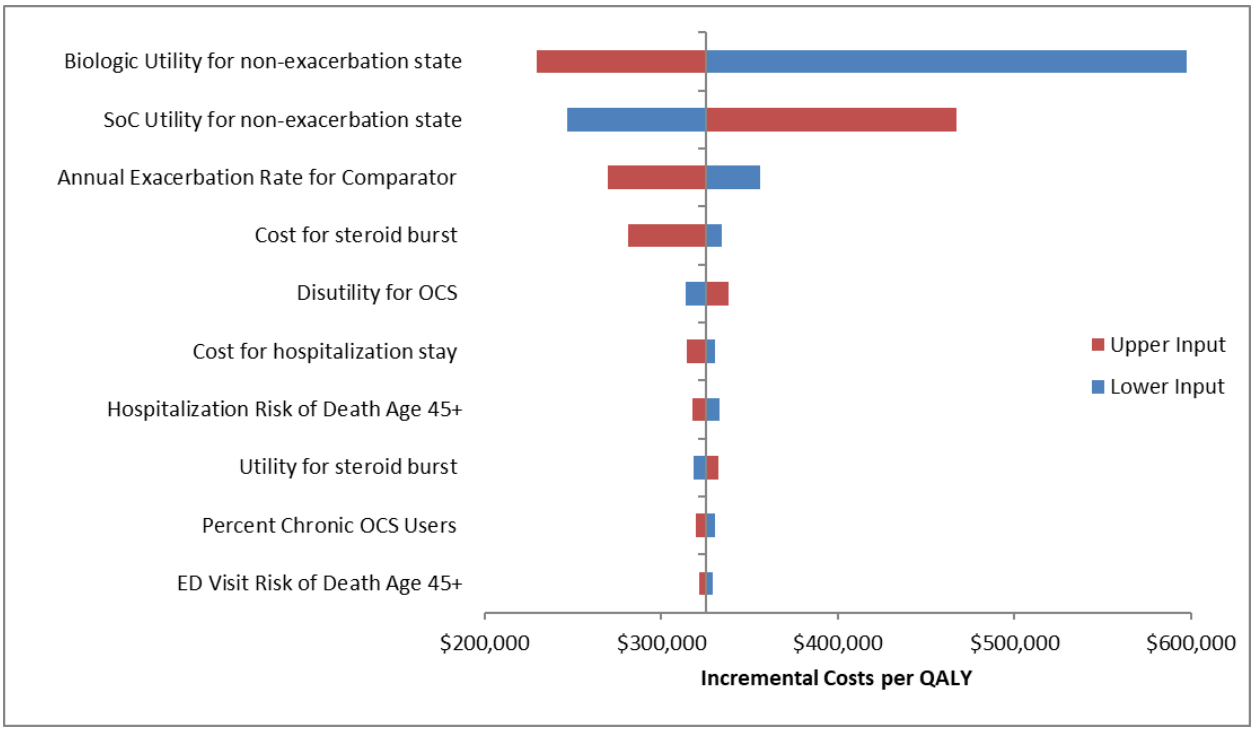


Figure E2. Reslizumab Tornado Diagram

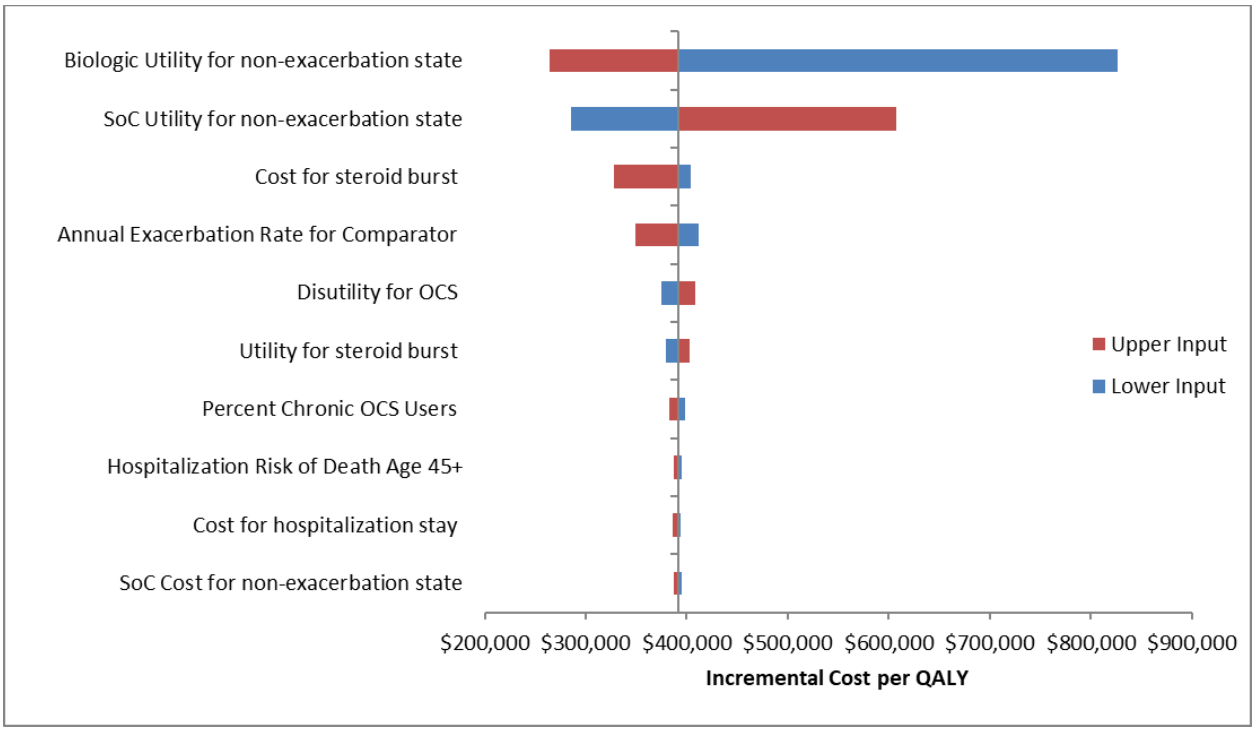


Figure E3. Benralizumab Tornado Diagram

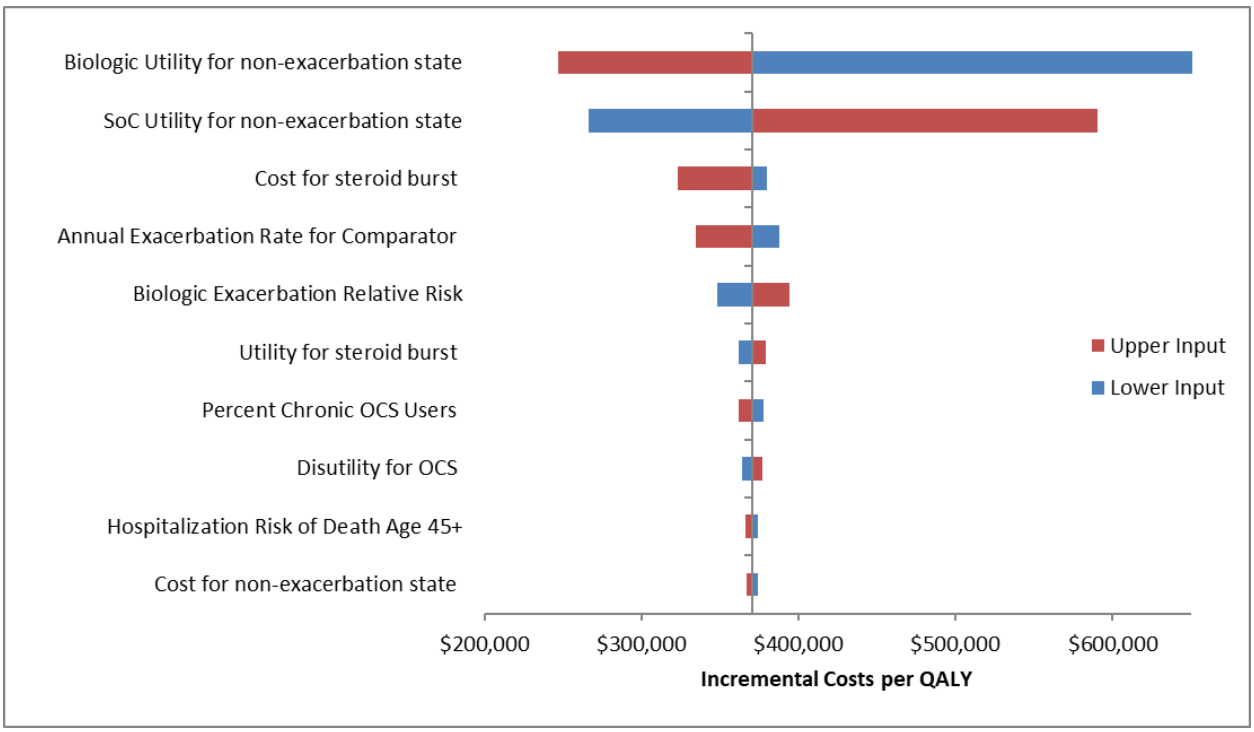
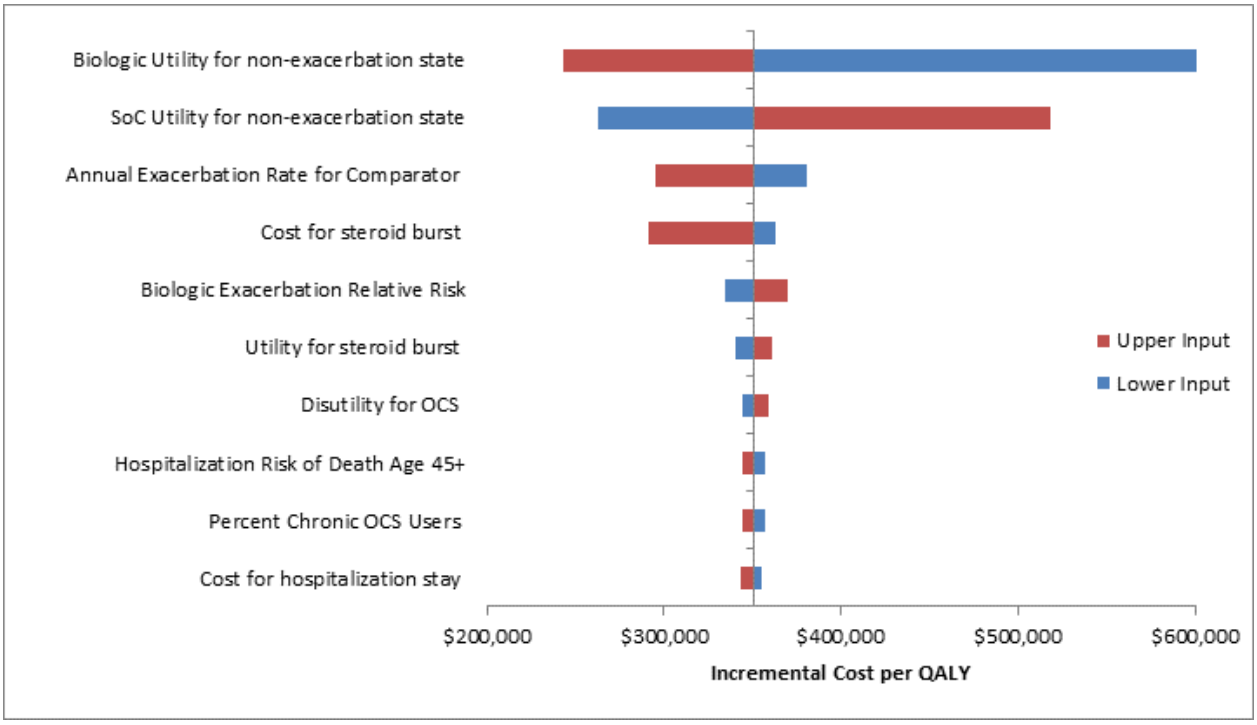


Figure E4. Dupilumab Tornado Diagram



Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on November 29, 2018 in St. Louis, MO. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Two speakers did not submit summaries of their public comments.

A video recording of all comments can be found here, beginning at minute 1:23:05. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Mark S. Forshag, MD, MHA
US Medical Expert – Respiratory, GlaxoSmithKline

Conflicts of Interest: Mark Forshag is a full-time employee of GlaxoSmithKline.

NUCALA remains the only IL-5 with up to 4.5 years of evidence that demonstrates positive clinical and humanistic outcomes. Accordingly, ICER's evidence rating for NUCALA was "high certainty of incremental net health benefit" and exploratory network meta-analysis demonstrated a significant clinical benefit for NUCALA versus placebo in a sub-set of clinically appropriate patients. This finding is consistent with GSK's clinical evidence package and FDA-approved product label for NUCALA for severe eosinophilic asthma.

GSK has identified several important limitations. First, the report assumes a payer's perspective, narrowing the analyses to potential offsets for existing healthcare costs, while limiting new costs. Thus, ICER's review omits critical considerations, including prescriber/patient experience and non-healthcare related patient/family impact.

Secondly, there is increased uncertainty in using model inputs from heterogenous patient populations and clinical metrics, and over-reliance on expert opinion. GSK reiterates our recommendations to: (1) report model outcomes as ranges and (2) release the complete model methodology to support stakeholder decision-making.

The third limitation is ICER's use of a model that applies common assumptions across five drugs as if representing a single class, whereas they represent four different mechanisms of action. A related issue extends to their unsupported market uptake assumptions for a new biologic with existing biologics approved. Assessment of the new therapy's budget impact is dependent on the degree it will replace existing biologics, versus being added to standard of care in biologic-naive patients.

GSK urges ICER to include transparent discussions of these limitations in the summary and body of their final report.

Margaret Garin, MD, MSCR
Director, Clinical Development, Global Research and Development, Teva

Conflicts of Interest: Margaret Garin is a full-time employee of Teva.

Teva strongly believes in patient-centered care, prescriber choice, and shared decision-making. Evidence suggests patients with asthma have individual qualities that may impact the value of one therapy over another for different patients. It is therefore imperative that prescribers have choices for personalizing therapy including intravenous (IV) reslizumab, the only biologic with weight-based dosing and consistent serum exposures across all body weights. Our trial evidence demonstrated early, consistent, and meaningful reductions in exacerbations, and improvements in FEV_1, asthma control, and quality of life, with sustained results up to 3 years. A real-world analysis showed similar OCS reductions for reslizumab as mepolizumab and benralizumab, and thus should be valued as such in cost-effectiveness evaluations.

Appropriate patient selection is paramount to optimize therapeutic value. Reslizumab's indication is in patients with severe asthma, a more restricted population than our clinical trials. ICER must prioritize the efficacy data for the subpopulation of patients that were severe and exacerbation-prone to understand the benefit and value in the indicated population. We agree that only responders should continue therapy, consistent with ICER's best-case scenario where the value of biologics neared commonly accepted cost-effectiveness thresholds; recent evidence demonstrates feasibility of assessment at 16 weeks after the first dose.[b]

Finally, patients with severe asthma may change their daily lives to avoid asthma triggers and may worry daily about when the next asthma exacerbation will occur. These are meaningful aspects of asthma that are not captured in trials for which reslizumab use can add significant value for patients.

Benjamin Kramer, MD
Vice President, Immunology and Ophthalmology, U.S. Medical Affairs, Genentech*

Conflicts of Interest: Benjamin Kramer is a full-time employee of Genentech.

We fundamentally believe in the value of Xolair and supporting patients' access to all innovative therapies. Xolair is uniquely distinguished from other asthma biologics. It is the first and only

[b] Bateman ED, Djukanović R, Castro M, Canvin J, Germinaro M, Noble R, Garin M, Buhl R. Predicting responders to reslizumab after 16 weeks of treatment using an algorithm derived from clinical studies of severe eosinophilic asthma patients. *Am J Respir Crit Care Med*. Published online: October 22, 2018 (doi:10.1164/rccm.201708-1668OC).

biologic indicated for the treatment of moderate-to-severe persistent allergic asthma in adults and children six years of age and older.

Xolair's extensive evidence base. There are >15 years of post-marketing experience with Xolair, culminating in >860,000 treated patient-years. There are >25 high-quality randomized controlled trials demonstrating Xolair's efficacy in reducing asthma exacerbations. These findings are supported by >25 observational studies that reflect long-term safety and real-world clinical and patient-reported outcomes. This body of evidence suggests a reduction of up to 80% in asthma exacerbation rates and up to 96% in hospitalization rates. Xolair's benefit has been demonstrated across a broad array of healthcare settings and patient sub-groups. Therefore, Xolair's clinical evidence rating should be higher than a B.

Limited comparability of asthma biologics. The understanding of asthma complexity and heterogeneity has evolved, with a recognition of allergic and eosinophilic phenotypes. Xolair's development program was different from more recently approved therapies. As a result, important patient characteristics that are highly related to trial endpoints, such as baseline lung function and exacerbation history, differed. This limits comparisons between biologics.

Importance of maintaining treatment options. Approximately 60-80% of asthma is allergic. Without Xolair, many allergic moderate-to-severe persistent asthma patients would have no biologic option after failing standard of care therapy.

We thank the asthma community for providing their perspectives on this important topic.

* In the U.S., Genentech and Novartis Pharmaceuticals Corporation work together to develop and co-promote Xolair.

Andreas Kuznik, PhD
Senior Director, Health Economics and Outcomes Research, Regeneron Pharmaceuticals
Representing Sanofi Genzyme/Regeneron

Conflicts of Interest: Andreas Kuznik is a full-time employee of Regeneron Pharmaceuticals.

1. ICER has used inappropriate clinical data for dupilumab in the base case of the model. Dupilumab was recently approved in the US as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥12 years with an eosinophilic phenotype or with OCS-dependent asthma. The annualized exacerbation rate ratios corresponding to the labeled populations are 0.44, 0.40, and 0.41 for the 200mg and 300mg doses in QUEST and the 300mg dose for OCS-dependent patients in the VENTURE study, whereas ICER used a single rate ratio of 0.52 in the model and presented rate ratios of 0.52 and 0.54 for the 200mg and 300mg doses, respectively, in Table ES2.

2. We reiterate the methodological importance of incorporating a response rule in the base case model. We believe that patients, physicians, and payers will observe response to treatment and discontinue therapy upon non-response. Response rules have been consistently used by ICER and NICE in their models across different symptomatic diseases. We recommend again that ICER use a response rule in their base case.
3. Finally, ICER assumes that patients in the standard of care (SOC) arm experience an annual exacerbation rate of 1.3, and this rate is assumed to be constant over a patient's lifetime. However, what is observed in the real world is a gradual increase in exacerbation risk among biologic-eligible patients on SOC that peaks well over 2 exacerbations annually prior to biologic initiation. We recommend that ICER apply more realistic exacerbation rates to the SOC arm over time.

Frank Trudo, MD, MBA
Vice President, Medical Affairs Respiratory, AstraZeneca

Conflicts of Interest: Frank Trudo is a full-time employee of AstraZeneca.

Severe asthma is a heterogeneous disease and a one-size-fits-all treatment approach is not effective. This has resulted in an over-reliance on systemic corticosteroids and for many, inadequate asthma control. Cumulative exposure to systemic corticosteroids is associated with an increased risk of related co-morbidities like diabetes, osteoporosis and other diseases. These risks increase based on the total exposure of systemic corticosteroids over time. Innovative treatments for severe asthma more precisely target key effector inflammatory cells, like the eosinophil, and have shown in clinical trials to reduce the rate of asthma exacerbations and reduce or eliminate chronic daily steroid use.

It is difficult to interpret the results of an analysis which assumes that every individual patient will achieve the same mean treatment response reported from clinical trials and then continue that very same medication indefinitely. In the real world, every patient is different, with most patients achieving clinical responses different than the mean. Through a shared decision-making process with patients, providers determine at each clinical encounter the best treatment plan based on clinical effectiveness and acceptable tolerability. This informs a medication continuation decision.

The output from this review will impact the lives of patients living with severe uncontrolled asthma. Providers should have therapeutic optionality and patients with severe uncontrolled asthma should have access to the treatments they need.

Bradley Becker, MD
Professor, Allergy and Immunology
St. Louis University School of Medicine, Departments of Pediatrics and Internal Medicine

Conflicts of Interest: None disclosed.

Children with asthma are a subpopulation which benefit from biologic therapies when used for the treatment of severe asthma with Type 2 inflammation. Eighty-five percent of children with asthma have allergic triggers or an eosinophilic phenotype.

In the Severe Asthma Research Program of the NIH, 30% of children reported a history of intubation for near-fatal respiratory failure.

The use of biologics for moderate to severe asthma is associated with significant decreases in morbidity and mortality.

The death of a child has a devastating lifelong impact on his family and caregivers. According to the CDC, about 200 kids died from asthma per year in the US.

Children with severe asthma, compared with adults, are more atopic, and have higher serum IgE and eosinophil levels.

In SARP: children had declines in lung function, greatest in those with aeroallergen sensitization. Studies suggest a subset of children with severe asthma have increased risk of developing COPD. Biologics for asthma decrease exacerbations which are felt to be major drivers for decreases in lung function.

ICER's analysis does not look at subpopulations such as pediatrics. It is likely QALY would improve if the analysis is limited to subgroups such as children.

I suggest the ICER Midwest CEPAC, consider these factors in reimbursement for biologic therapies for the treatment of type-2 asthma in children.

Tonya Winders
President and CEO, Allergy & Asthma Network

Conflicts of Interest: Allergy & Asthma Network has received funding for unbranded disease education & awareness in excess of $5,000 from AstraZeneca, Genentech, GSK, Sanofi Genzyme, and Teva.

Tonya Winders, CEO of Allergy & Asthma Network, presented the voice of the 1-2M patients living with severe asthma by highlighting four emotional patient stories. From ER visits, hospitalizations, disability, etc. to oral steroid side effects, relational and financial toil, the patient journeys shared

allowed the panel to hear how this disease is limiting so many lives beyond what the ICER value framework currently accounts.

Winders implored ICER to reconsider its value assessment by recognizing more patient-reported outcomes vs QALY's and to better account for the heterogeneity and complexity of the disease rather than relying on clinical trial data which was never intended for cost effectiveness analysis. Moreover, she challenged ICER to move away from solely a healthcare sector perspective to a patient-centered perspective.

In a time of unprecedented scientific advancements and personalized medicine in asthma, the ICER report is likely to unnecessarily limit access to innovation based on minimal "exploratory" data. It is imperative for all community stakeholders (Policymakers, Manufacturers, Healthcare Providers, & Patients) to collaborate to ensure the most appropriate treatment to the most appropriate patient at the most appropriate time and at the most affordable cost to the system. This will certainly take compromise by all parties and can only be accomplished by placing patients at the center of the conversation. The "small net benefit" noted by ICER's evaluation of the asthma biologics is inconsistent with testimonials of lives changed due to these treatments and should not be used to undermine the patient/physician shared decision-making process.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the November 29, 2018 public meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ellie Adair, MPA	ICER	None
Jonathan D. Campbell, PhD	University of Colorado Skaggs School of Pharmacy	None
Maggie O'Grady, BS	ICER	None
Steve Pearson MD, MSc	ICER	None
David Rind, MD, MSc	ICER	None
Jeffrey A. Tice, MD	University of California, San Francisco	None

Table G2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	St. Louis University	*
Ryan Barker, MSW, MPPA	Missouri Foundation for Health	*
Aaron Carroll, MD, MS	Indiana University School of Medicine	*
Don Casey, MD, MPH, MBA	IPO4Health, Medecision	*
Rena Conti, PhD	University of Chicago	She and family members have been treated or likely are candidates for treatment with these biologics.
Gregory Curfman, MD	Journal of the American Medical Association (JAMA)	*
Stacie Dusetzina, PhD	Vanderbilt University School of Medicine	*
Elbert Huang, MD, MPH	University of Chicago	*
Jill Johnson, PharmD	University of Arkansas for Medical Sciences	*
Timothy McBride, PhD	Washington University in St. Louis	*
Scott Micek, PharmD	St. Louis College of Pharmacy	*
Harold Pollack, PhD	University of Chicago	*
Rachel Sachs, JD, MPH	Washington University in St. Louis	*
Timothy Wilt, MD, MPH	Minneapolis VA Center for Chronic Disease Outcomes Research	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participant COI Disclosures

Name	Organization	Disclosures
Mario Castro, MD, MPH	Washington University School of Medicine	Receives grant funding from AstraZeneca, GSK, and Sanofi-Aventis. Consultant for Genentech, Teva, and Sanofi-Aventis. Speaker for AstraZeneca, Genentech, Regeneron, Sanofi, and Teva.
David Evan	Teva	Full-time employee of Teva.
Marsha Fisher, MD, FACOG	Anthem BCBS of Missouri	Full-time employee of Anthem BCBS of Missouri.
Mark S. Forshag, MD, MHA	GlaxoSmithKline	Full-time employee of GlaxoSmithKline.
Jeremy Fredell, PharmD, BCPS	Express Scripts	Full-time employee of Express Scripts.
Benjamin Kramer, MD	Genentech	Full-time employee of Genentech.
Andreas Kuznik, PhD	Regeneron	Full-time employee of Regeneron.
Donna J. Matlach, DMin, MM, CDA	Allergy and Asthma Network	AAN receives funding from AstraZeneca, Genentech, GSK, Sanofi Genzyme, and Teva.
Kenny Mendez, MBA	Asthma and Allergy Foundation of America	AAFA receives funding from AstraZeneca, Genentech, GSK, Sanofi/Regeneron, and Teva.
Kaharu Sumino, MD, MPH	Saint Louis VA Medical Center; Washington University School of Medicine	None.
Frank Trudo, MD, MBA	AstraZeneca	Full-time employee of AstraZeneca.