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

Draft Evidence Report

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Prepared for

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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. Varun Kumar developed the budget impact model. Ellie Adair authored the section on coverage policies and clinical guidelines. 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.

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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/.

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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
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

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] Individuals 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.[4] 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]

There are a number of treatments available for asthma.[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. Additional therapies for severe asthma include leukotriene inhibitors, theophylline, omalizumab, mepolizumab, reslizumab and benralizumab. 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.[5] Treatment is progressive from Step 1 (SABA as needed) to Step 3 (low dose ICS + LABA) to Step 5 (high dose ICS + LABA with consideration of omalizumab in patients with allergic asthma or one of the three drugs targeting the IL-5 pathway (mepolizumab, reslizumab and benralizumab) in patients with eosinophilic asthma). Finally, Step 6 is high dose ICS + LABA + OCS.

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.[6] These cells secrete IL-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[7,8] Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma.[9,10]

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, 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[11]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[12]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[13]
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[14]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	*PDUFA date 10/20/2018[15]

*Dupilumab does not have an FDA indication for asthma at this time.

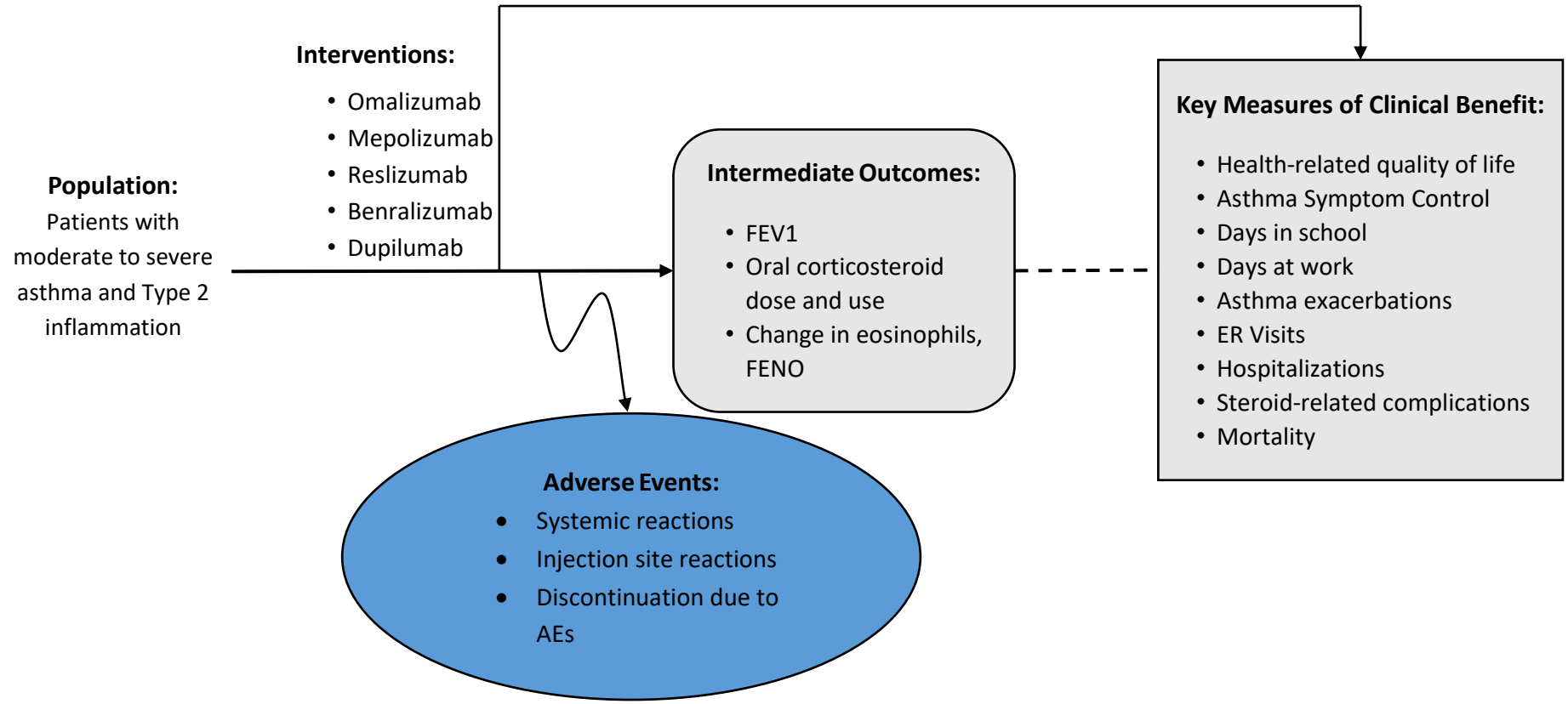
1.2 Scope of the Assessment

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.[16]

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.[4] 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.[4,17] 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 (FEV1 <80% predicted); or poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test < 20).[4] 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).

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.[4]

Moderate asthma is defined as asthma that is controlled with low dose ICS plus LABA.[17]

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)[4]

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, FEV1, 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.

FEV1: The FEV1 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.[18] 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.[18]

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.[18]

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." American Academy of Allergy Asthma & Immunology, 2012, 119}

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 awaits FDA approval 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.[19] 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.[20] 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 [21-26]

	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
Resilizumab		
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, National Institutes of Health, and National Heart, Lung, and Blood Institute jointly release 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:[27]

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.[28]

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.

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 FEV1 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.[29,30] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31,32] 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 was extracted into evidence tables (Appendix Tables D1-D5).

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."[33]

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 D1-5. 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.[34,35] 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 attempted to define a population that was similar enough in baseline characteristics to conduct a network meta-analysis for patients with baseline eosinophil counts ≥ 300. Given the residual heterogeneity across studies, we consider this analysis exploratory.

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[35] and the 2017 Cochrane Review for mepolizumab, reslizumab, and benralizumab.[34] For mepolizumab, reslizumab, and benralizumab we only used the results for patients with eosinophilic asthma to match the FDA indications for those three drugs.[12-14]

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 versus 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	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 beta$_2$-adrenergic agonist; OCS = Oral corticosteroids; SoC = Standard of care; - = Not required.

In addition, the definition of an exacerbation differed between studies (Table 3.2).

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

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab[36, 3736,3736,3736,3734,35]	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, because this group was more homogenous and several trials reported that their biologic therapy was more effective in patients with eosinophil counts ≥ 300 cells/ µL.[38-40]

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[34,35] for each of the drugs are summarized in Table 3.3 below in addition to the estimates for dupilumab from the pivotal trial.[38] 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.[38,39,41] 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	0.52 (0.41-0.66)
Dupilumab 300 mg	0.54 (0.43-0.68)

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	0.35 (0.08-0.62)
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

As can be seen in Table 3.4 above, the average improvement for all five drugs compared with placebo is modest and none of them reach the minimally important difference, although all were statistically significant. Only the 95% CI for mepolizumab includes the minimally important difference. These 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, FEV1, 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 AQLQ 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)[42] and the DREAM study of mepolizumab (mean ACQ 4.2).[43]

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 primarily been used in COPD, but has been validated in patients with asthma. 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.

Surrogate markers of response

Several surrogate markers were reported in the majority of trials.

Pre-Bronchodilator FEV1: The forced expiratory volume in one second (FEV1) is a measure of obstruction to the flow of air in the lungs. When asthma is under poor control, the FEV1 is lower than when it is under good control. All of the drugs significantly improved FEV1 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 FEV1 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)

FEV1: 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 reduction in asthma exacerbations, improvements in quality of life measure, or improvements in FEV1. 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 a greater reduction in asthma exacerbations nor greater improvements in quality of life.

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 trends towards greater drug discontinuation rates due to adverse events for omalizumab and 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	1.41 (0.84-2.37)
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 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: 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 0.2%. The estimated rate of anaphylaxis for omalizumab is 0.3%.

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 effects of reslizumab are nasopharyngitis, upper respiratory tract infections and myalgias.

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 patents.[44,45] 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).[45] 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.[44] 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,[46] mepolizumab,[47] benralizumab,[48] and dupilumab[49] 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.[46] 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.[47] 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.[48] 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 (p<0.001 for both comparisons).

The LIBERTY ASTHMA VENTURE study randomized 210 patients with severe asthma on OCS to dupilumab 300 mg SC every two weeks for 24 weeks.[49] 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

Three of the five biologic drugs considered in this review are indicated for eosinophilic asthma and the other two drugs have 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).[38,39] Because the benefits seemed greater in this population and because it may represent a more homogenous population, we performed a network meta-analysis in this subgroup. We requested data from manufacturers in the subgroup of patients with eosinophils ≥ 300 cells/µL and two or more exacerbations in the year prior to randomization, but received data too late for the draft review. We will update our NMA with the additional data for the final report.

Table 3.11: Relative Rates 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)
Dupilumab 200 mg	0.93 (0.58-1.47)	0.34 (0.24-0.48)
Dupilumab 300 mg	1.15 (0.75-1.77)	0.33 (0.23-0.45)

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

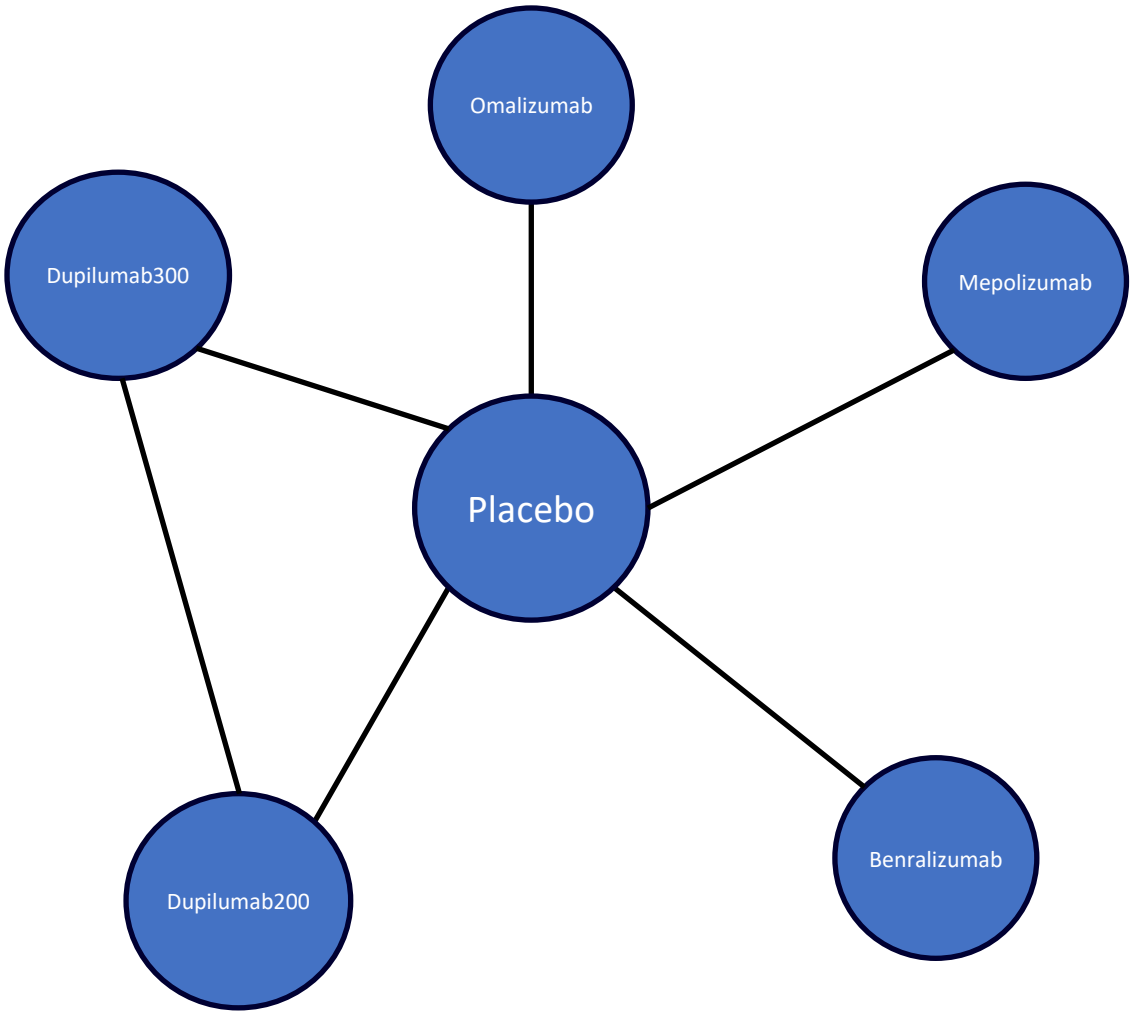


Table 3.12 below shows the pairwise comparisons for all of the drugs as well as placebo.

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

Dupilumab300						
0.92 (0.46-1.71)	**Dupilumab200**					
0.66 (0.27-1.44)	0.71 (0.31-1.61)	**Reslizumab**				
0.62 (0.23-1.36)	0.67 (0.26-1.49)	0.94 (0.40-1.96)	**Mepolizumab**			
0.58 (0.26-1.31)	0.63 (0.30-1.48)	0.88 (0.45-1.98)	0.94 (0.48-2.28)	**Omalizumab**		
0.51 (0.21-1.11)	0.55 (0.24-1.23)	0.78 (0.36-1.64)	0.83 (0.39-1.9)	0.88 (0.39-1.69)	**Benralizumab**	
0.30 (0.15-0.54)	**0.33 (0.17-0.60)**	**0.46 (0.26-0.78)**	**0.49 (0.28-0.91)**	**0.52 (0.29-0.80)**	**0.59 (0.35-0.99)**	**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, each of the drugs is significantly more effective than placebo (last row, all in bold) in reducing asthma exacerbations, but none of the drugs are significantly better than any of the other active therapies. The estimates for dupilumab are slightly better than the estimates for the other therapies, but the differences are not significant. The estimates for the RR for dupilumab are better than those reported in the full trial, but the NMA estimates for the other drugs are similar to their overall estimates, which is expected for the anti-IL-5 drugs, because they are indicated in eosinophilic asthma and we used the estimates in the Cochrane meta-analyses for eosinophilic asthma. However, we expected omalizumab to have a greater reduction in exacerbation rates. Because of the residual heterogeneity of the underlying patient populations and the definitions of exacerbations used across trials, we consider this to be an exploratory analysis. We hope to have more homogenous data from the manufacturers prior to the final report.

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.

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.

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.[50] They assert that they regard the treatments targeting Type 2 inflammation "as essentially equivalently effective treatments." They call for researches 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.[50]

3.4 Summary and Comment

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 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. 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 data. 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 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. 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. 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 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. 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 (only one trial with 24 weeks or more follow-up). 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). Reslizumab does carry a black box warning for 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. 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. 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 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. The common AEs reported in studies of dupilumab for atopic dermatitis were not replicated in the trials for asthma. Because the drug has not yet been approved, we lack clear guidance on the final dosing recommendations and patient indications and we have no real-world observational data to support the findings of the randomized trials. 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.[51] 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.[51] The model framework and assumptions are described in detail below.

4.2 Methods

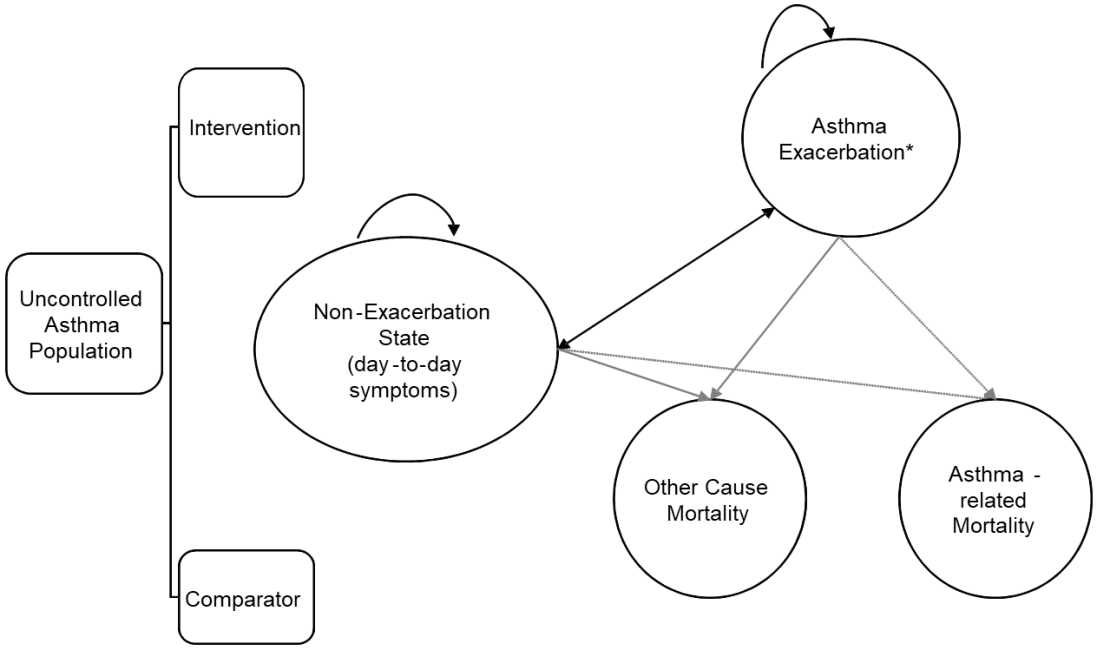
Model Structure

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.[52,53]

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[51,53] 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.[52,54-58] 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.[54,59,60] 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[52,56] and asthma guidelines that suggest new exacerbation events should only be considered after at least a 7-day period from a prior event.[61]

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 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)[62]
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 300 mg by subcutaneous injection once every two weeks

Dupilumab dosing for asthma is pending approval by the Food and Drug Administration (FDA); if and when approved by the FDA, any adjustments in dosing schedule will be made for future versions of this report in accordance with the drug's prescribing information.

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 versus SoC alone due to potential improvements in day-to-day symptoms.	Without direct elicitation of utilities in trials comparing biologic plus SoC versus 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.[63] A manufacturer submission to NICE used a similar approach.[64] Although other utility relationships are known for the Asthma Quality of Life Questionnaire,[65] 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.[64] However, given heterogeneity across treatment responder definitions, stakeholder comments, limited comparative outcomes evidence tied to treatment responders versus 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.[64,66]
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.[67]
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.[54,64]
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 versus 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 analyses.

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.[54,64]

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)[52]	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[36]	300 mg every 2 weeks[38]
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%)[46]	0.68 (46% vs. 68%)[47]	1.0 (Not reported)*	0.61 (41% vs. 67%)[48]	0.46 (31% vs. 67%)[49]

*For evidence "Not reported," no difference was assumed (i.e., relative reduction of 1.0) between biologic plus SoC versus 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)[35]	0.45 (0.36-0.55)[34]	0.43 (0.33-0.55)[34]	0.59 (0.51- 0.68)[34]	Not reported; assumed 0.54 (0.43-0.68)[38]
Rate Ratio for Exacerbations Resulting in ED visit (without hospitalization)	0.40 (0.19-0.82)[68]*	0.36 (0.20-0.66)[34]	0.67 (0.39-1.17)[34]	0.68 (0.47-0.98)[34]	Not reported; assumed 0.54 (0.43-0.68)[38]
Rate Ratio for Exacerbations Resulting in Hospitalization	0.16 (0.06-0.42)[35]	0.31 (0.13-0.73)[34]	0.67 (0.39-1.17)[34]	0.68 (0.47-0.98)[34]	Not reported; assumed 0.54 (0.43-0.68)[38]

*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.

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%[68-70]
Proportion of Exacerbations Resulting in ED visit (without hospitalization) †	5%[68-70]
Proportion of Exacerbations Resulting in Hospitalization**	5%[68-70]

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).[64,66,71,72] 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%).[71] 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.[64] 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.[72] 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,[66] 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.[69] and Chupp et al.[73] reported on the St George's Respiratory Questionnaire (SGRQ) for mepolizumab plus SoC versus SoC alone.[34] We identified a published mapping between mean total SGRQ scores and the EQ-5D. The mean total SGRQ score of 38.9 for SoC[69] and 31.5 for mepolizumab plus SoC based on the pooled study mean difference[34] 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).[63]

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.[63] 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.[65] 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.[42,52] 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 versus SoC (95% CI)	0.26 (0.05-0.47)[35]	AQLQ: 0.35 (0.08-0.62)[74] SGRQ: -7.4 (-9.5 to -5.3)[34]	0.28 (0.17-0.39)[34]	0.23 (0.11-0.35)[34]	0.26 (0.12-0.40)[38]
Non-Exacerbation Mean Health State Utility for biologic plus SoC vs. SoC alone (SE)*	Biologic plus SoC: 0.830 (0.020) SoC: 0.768 (0.015)	Biologic plus SoC: 0.830 (0.010) SoC: 0.768 (0.015)	Biologic plus SoC: 0.830 (0.020) SoC: 0.768 (0.015)	Biologic plus SoC: 0.830 (0.020) SoC: 0.768 (0.015)	Biologic plus SoC: 0.830 (0.020) SoC: 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 versus 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 versus SoC alone).[75] 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.[75] 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.[76]

The disutility of chronic OCS for the proportion of patients using >5 mg daily (-0.023)[55] 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[75]
Exacerbation Requiring ED Visit*	-0.15	Lloyd et al. 2007[75] and assumption
Exacerbation Requiring Hospitalization*	-0.20	Lloyd et al. 2007[75]
Chronic Oral Corticosteroid Use†	-0.023	Norman et al. 2013[55]

*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. We found estimates of net price for only some and not all biologics in the SSR Health database. We hence requested net price data from the five manufacturers of these biologics. However, this information was supplied to us only by the manufacturers of omalizumab and mepolizumab. We thus used manufacturer-reported net price for omalizumab and mepolizumab whereas we used FSS for reslizumab, benralizumab, and dupilumab.[77]"

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 300 mg
Federal Supply Schedule (FSS)	$965.76	$2,553.97	$847.04	$4,728.23	$2,774.65
Wholesale Acquisition Cost (WAC)	$1,084.66	$2,868.67	$878.80	$4,752.11	$2,931.54
Manufacturer Net Price	$802.64*	$2,272†			

*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"
‡Dupilumab dosing for asthma is pending approval by the Food and Drug Administration (FDA); once available by FDA, any adjustments in dosing schedule and corresponding unit price will be made within this report.

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.[78] All costs were inflated to 2018 levels using the health care component of the personal consumption expenditure index,[79] in accordance with the ICER Reference Case.[80]

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.[53]

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.[67] 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.

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[78]
Exacerbation-Related ED Visit (SD)	$2,072 (2,751)	Suruki et al. 2017[78]
Exacerbation-Related Hospitalization (SD)	$9,053 (7,257)	Suruki et al. 2017[78]
Annual Cost for SoC (95% interval)	$6,227 ($5079, $7505)	Whittington et al. 2018[53]
Annual Cost of Long-Term Oral Corticosteroid Use with Adverse Events (SD assumed)	$7983 ($7983)	Lefebvre et al. 2017[67]
Intravenous Treatment Administration (1st Hour) for Reslizumab	$144.72 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 96413)[81]
Office Visit Treatment Administration for Subcutaneous Office-Administered Biologics	$74.16 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 99213)[81]

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.[82] 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).[83,84] 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[83]
Hours missed per week (Asthma Biologic)	1.46	DoF[84]
Hours missed per week (Standard of Care)	3.09	DoF[84]

*DoF: Data on File

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 two additional scenario analyses for the draft 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 from omalizumab studies (see below).

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: 0.60 for omalizumab versus SoC; 0.48 for mepolizumab versus SoC; 0.46 for reslizumab versus SoC; 0.58 for benralizumab versus SoC; and 0.31 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 1.44 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).[55]

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 4.12-4.16 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. Total lifetime discounted costs were slightly higher for dupilumab at $897,000 than the other agents; dupilumab dosing and unit cost may change upon FDA approval of an asthma indication. 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

Omalizumab: Base-Case Discounted Costs				
	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Omalizumab[¶]	$694,000	$41,500	$735,000	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

Mepolizumab: Base-Case Discounted Costs				
	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

[¶] Price = $2,272* (100 mg)

*Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns"

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

Reslizumab: Base-Case Discounted Costs				
	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Reslizumab[¶]	$751,000	$50,000	$801,000	16.06
SoC	$120,000	$73,300	$193,000	14.59

QALYs: Quality-adjusted life years, SoC: Standard of care

[¶] Price = $847.04 (100 mg/ml vial)

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

Benralizumab: Base-Case Discounted Costs				
	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Benralizumab[¶]	$728,000	$45,800	$774,000	16.00
SoC	$120,000	$73,300	$193,000	14.59

QALYs: Quality-adjusted life years, SoC: Standard of care

[¶] Projected price = $4,728.23 (30 mg)

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

Dupilumab: Base-Case Discounted Costs				
	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Dupilumab[¶]	$859,000	$38,400	$897,000	16.10
SoC	$120,000	$73,300	$193,000	14.59

QALYs: Quality-adjusted life years, SoC: Standard of care

[¶] Projected price = $2,774.65 (2*300 mg)

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. With annual price increases, we observed increases in base-case discounted incremental results.

Table 4.16. Base-Case Discounted Incremental Results

Base-Case Discounted Incremental Results					
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY gained (vs. SoC)	$313,000 / QALY	$344,000 / QALY	$412,000 / QALY	$412,000 / QALY	$464,000 / QALY

QALY: Quality-adjusted life year, SoC: Standard of care

Table 4.17. Base-Case ICER and Annual Price (side-by-side)

	Base-Case ICER	Annual Price	Notes
Omalizumab	$313,000	$28,900	Manufacturer provided net price
Mepolizumab	$344,000	$29,500	Manufacturer provided net price
Reslizumab	$412,000	$30,500	FSS price
Benralizumab	$412,000	$30,800	FSS price
Dupilumab	$464,000	$36,000	Used FDA approved dosing and FSS price

Lifetime Annualized Clinical Outcomes

Appendix Tables E.2- E.6 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 E.1- E.4).

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 SoC

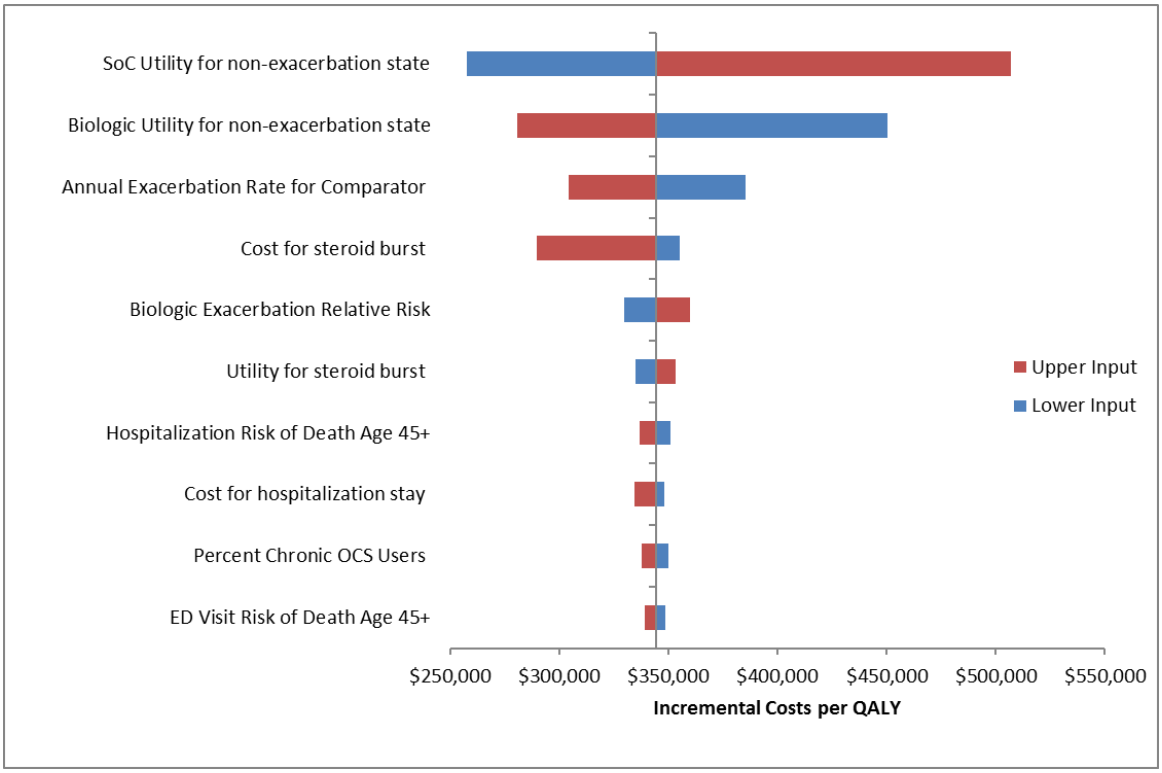


Table 4.18. Tornado Diagram Inputs and Results for Mepolizumab versus Standard of Care

Input Name	Lower ICER	Upper ICER	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, ICER: Incremental cost-effectiveness ratio, SoC: Standard of care
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER 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. Lastly, 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.

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

	Incremental Costs	Incremental QALYs	Incremental CE Ratio per QALY
Omalizumab	$503,000	1.73	$291,000 / QALY
Mepolizumab	$523,000	1.63	$320,000 / QALY
Reslizumab	$568,000	1.48	$385,000 / QALY
Benralizumab	$541,000	1.41	$384,000 / QALY
Dupilumab	$665,000	1.52	$438,000 / QALY

CE: Cost-effectiveness, QALY: Quality-adjusted life year, SoC: Standard of care

Table 4.21. Treatment Responder Scenario Incremental CE Ratio

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY gained (vs. SoC)	$ 205,000/ QALY	$ 214,000/ QALY	$234,000 / QALY	$222,000 / QALY	$269,000 / QALY

CE: Cost-effectiveness, QALY: Quality-adjusted life year, SoC: Standard of care

Table 4.22. Eosinophils ≥ 300 Count Incremental CE Ratio

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY gained (vs. SoC)	$354,000 / QALY	$355,000 / QALY	$403,000 / QALY	$388,000 / QALY	$401,000 / QALY

CE: Cost-effectiveness, 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 4.23. 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	$5,800	$10,100	$14,400
Mepolizumab	$5,100	$9,200	$13,400
Reslizumab	$2,900	$6,500	$10,400
Benralizumab	$4,700	$8,300	$11,900
Dupilumab	$3,900	$7,800	$11,400

QALY: Quality-adjusted life year

Table 4.24. Threshold Unit Price Results

Intervention	Unit	WAC per Unit	FSS or 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*	$160	$280	$400
Mepolizumab	100 mg	$2,868.67	$2,272†	$390	$710	$1,030
Reslizumab	100 mg/ml vial	$878.80	$847.04	$80	$180	$290
Benralizumab	30 mg	$4,752.11	$4,728.23	$720	$1,270	$1,820
Dupilumab‡	2 x 300 mg	$2,931.54	$2,774.65	$300	$600	$880

*Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. 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)".
†Average net sales price is inclusive of WAC rebates, allowances, and returns
‡Dupilumab dosing for asthma is pending approval by the Food and Drug Administration (FDA); if and when approved by the FDA, any adjustments in dosing schedule and corresponding unit price will be made within this report in accordance with the drug's prescribing information.

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.[51,52,85,86] 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 1.7 times the 2009 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 ($735,000 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 $313,000 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.[87] 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 versus SoC) rather than the utility improvement associated with all those who

received omalizumab (0.063 versus SoC). Exacerbation-related disutility values in both models were derived from the same source, Lloyd et al., which was conducted in the UK.[75] 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.[51] Model structure for this review followed the same structure as seen in Campbell et al.'s 2010 publication.[52] 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.[53]

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.[64] 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 scenario was including the potential costs and benefits of biologic treatment responders (and non-responders). In what might be interpreted as a best-case scenario based on best-available comparative evidence, we found incremental cost-effectiveness findings that ranged from $205,000/QALY for omalizumab to $269,000/QALY for dupilumab. 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 treatment responder scenario 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,[64,88] the

patient populations in their reports are based on the United Kingdom, not the United States, which limits the potential adaptability of our model.

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 a *what if* scenario that efficiently identified treatment responders and only continued long-term biologic therapy in those responders. Therefore, 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 and requires a visit to a medical center for each dose.

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

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/about November 13, 2018.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab in adults and children six years of age and older with persistent moderate-to-severe uncontrolled asthma in the US. We used the WAC, an estimate of discounted WAC, 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 to find the average number of patients with asthma.[89,90] 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.[91,92] 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.[93] 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.[94] We applied this estimate more broadly to the moderate-to-severe asthma population, to arrive at an estimate of approximately 1.3 million patients over five years, or approximately 257,000 patients each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[95] 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.[96,97] 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), discounted WAC ($36,070 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($11,440 per year, $7,800 per year, and $3,900 per year, respectively) compared to current treatment mix.

[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.

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

	Average Annual Per Patient Budget Impact				
	At WAC	At Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$47,318	$45,305	$20,992	$17,399	$13,550
Current Treatment Mix*	$44,039				
Difference (Dupilumab – Current Treatment Mix)	$3,279	$1,266	($23,047)	($26,640)	($30,490)

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

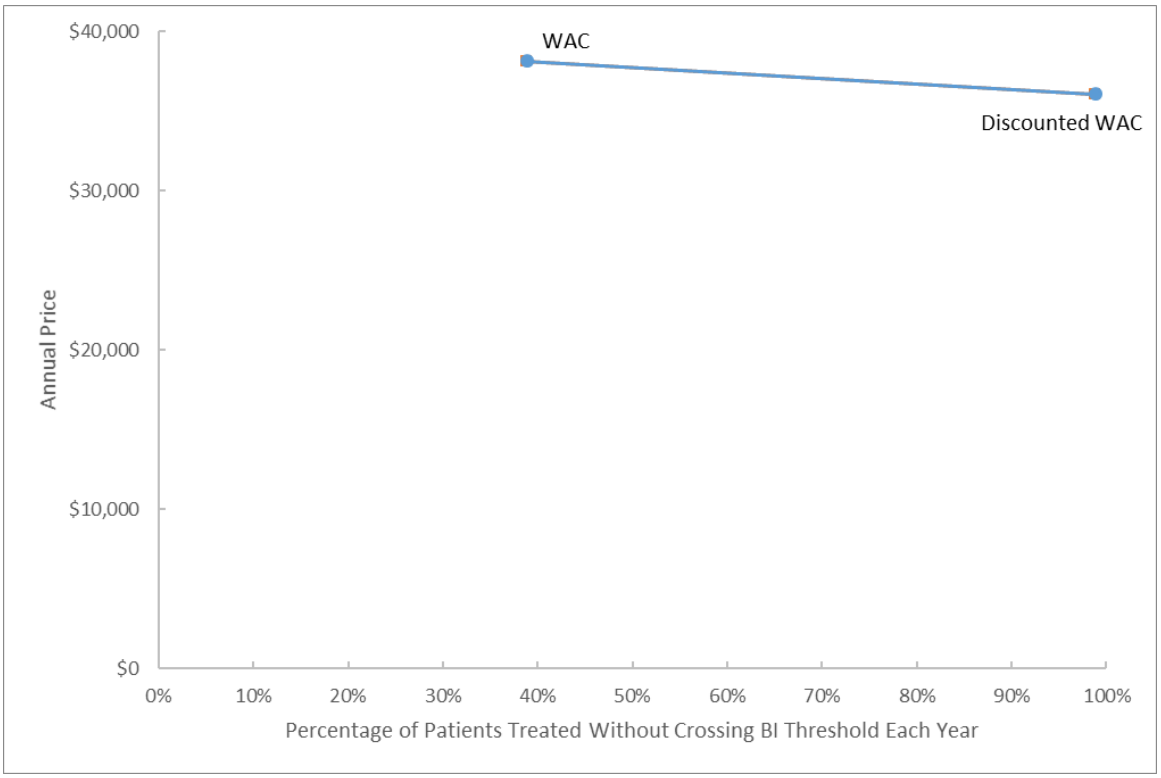
*27% of target population on biologics and 73% on standard of care. Market share among biologics: reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2%, and omalizumab – 74.9%

() – Cost-saving

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $3,300 per year, and approximately $1,300 per year using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug were estimated to be cost saving, ranging from approximately $23,000 per patient in savings using the annual price to achieve $150,000 per QALY to approximately $30,500 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). When compared to individual biologics at their respective discounted WAC and associated health care costs, using dupilumab will result in additional costs at the per patient and population level at its WAC and discounted WAC, but will result in cost-savings at the three WTP threshold prices.

At dupilumab's WAC and discounted WAC, 39% and 99% of the eligible population could be treated before the total budget impact exceeds the ICER annual budget impact threshold (Figure 7.1). While the difference in the per patient budget impact is only approximately $2,000 per year, the substantial difference in the percentage of eligible population that can be treated is due to the size of the patient population. At its 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.

Figure 7.1. Potential Budget Impact Scenarios at Different Prices of Dupilumab to Treat Moderate-to-Severe Uncontrolled Asthma in Adults and in Children ≥ Six Years of Age



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This is the first ICER review of omalizumab, reslizumab, benralizumab, and dupilumab for the treatment of asthma. ICER previously reviewed mepolizumab for asthma treatment in 2016. This report can be viewed on ICER's website: https://icer-review.org/material/asthma-final-report/.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

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

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

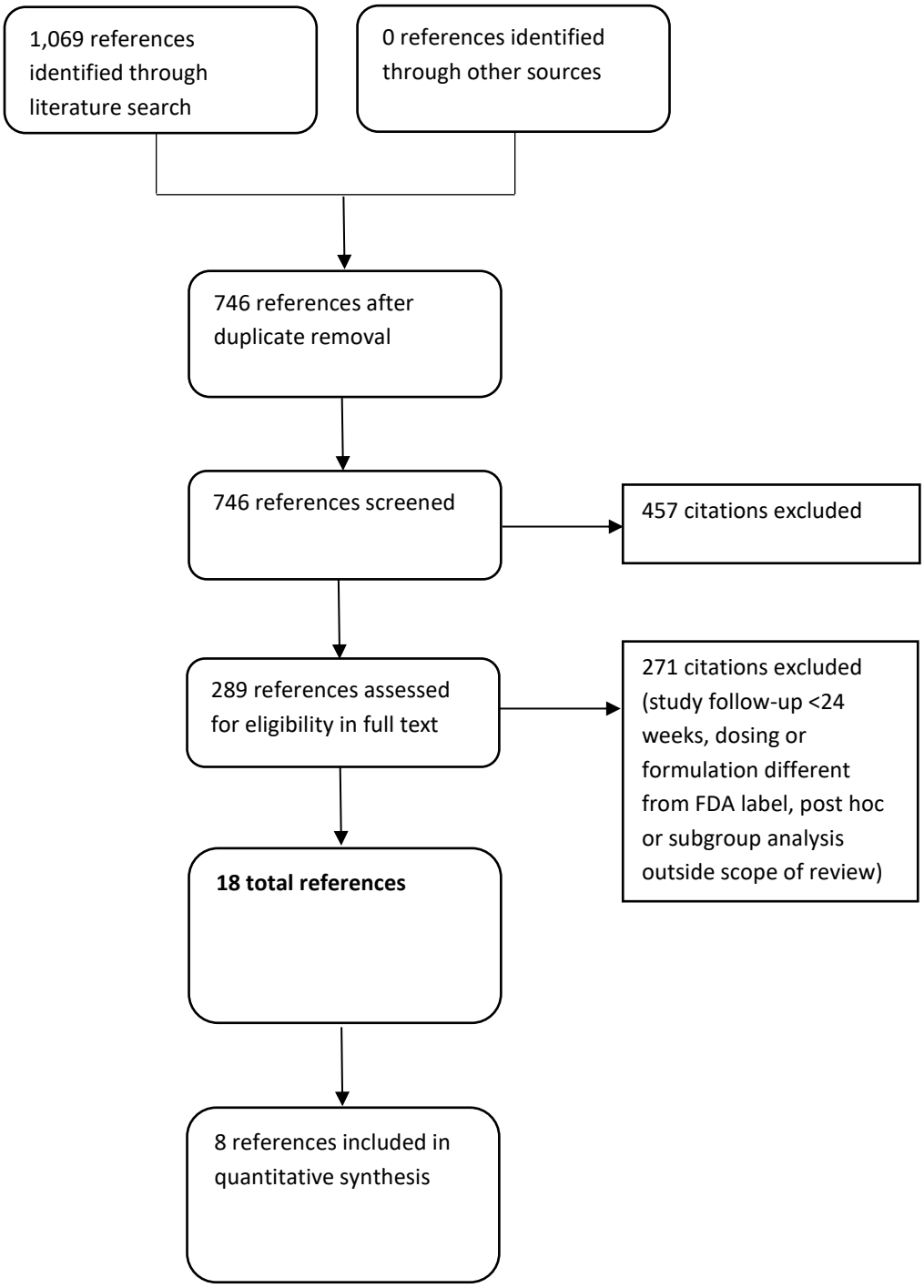
Table A2. Search Strategy of Medline and Cochrane Central Register of Controlled trials (via Ovid)

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 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.

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 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.

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 disase 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 repiratory 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

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	<u>Inclusion Criteria:</u> •Age ≥12 years •Weight ≥40kgs •Persistent airflow obstruction •Documented or high likelihood of eosinophilic asthma •Regular treatment with high dose ICS in 12 months prior to Visit 1 •Current treatment with additional controller medication for ≥3 months •History of ≥2 exacerbations requiring systemic corticosteroid in 12 months prior to Visit 1 <u>Exclusion Criteria:</u> •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	<u>Primary Outcome:</u> •Clinically significant exacerbations <u>Secondary Outcomes:</u> •Time to first clinically significant exacerbation •Mean change from baseline in St. George's Respiratory Questionnaire •Number of exacerbations requiring hospitalization or ED visits •Number of 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

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 repiratory 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

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 •Treatment with 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 requiredtreatment 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 that has not been treated/ failed to respond to treatment •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

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 medicationor high-dose ICS with or without second controller, for at least 3 months •Pre-bronchodilator FEV1≤95% of predicted normal or pre bronchodilaror 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 corticosterois 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 F2)[33] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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

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

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

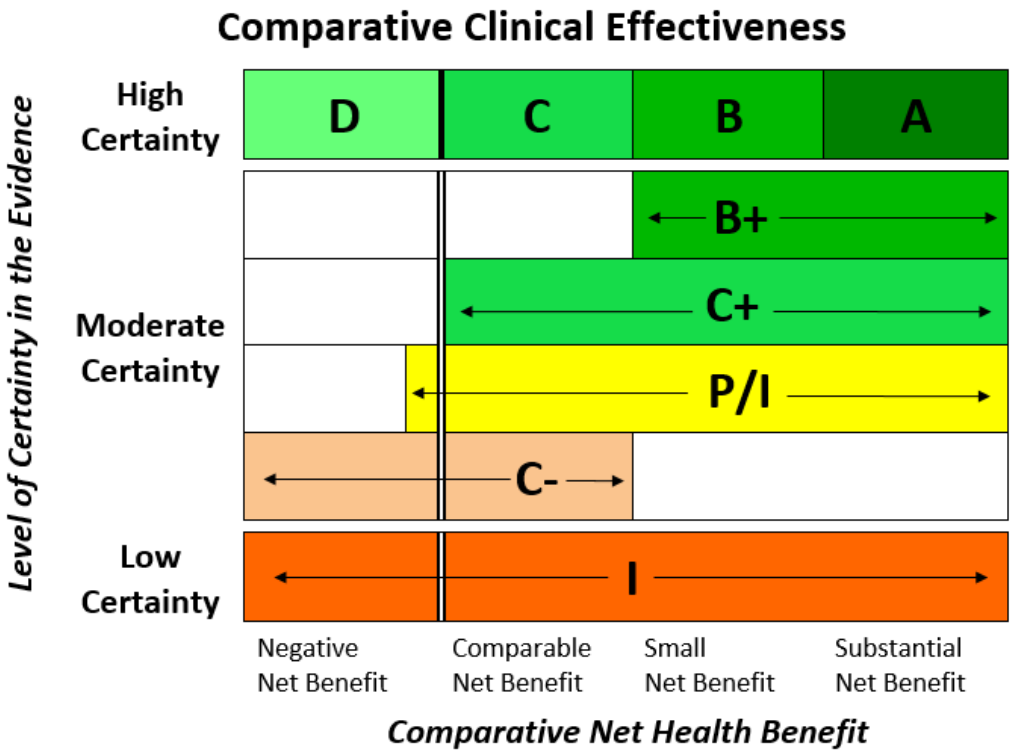
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

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.[98]

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[99] **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[42] **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[44] **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[100] (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[101] (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[39] (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[102] 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[43] 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[69] **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[73] **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[47] **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[70] (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[36] **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 excerbations	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[37] **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[48] **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[103] (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[38] **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[49] 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 Critera	Sputum Eosinophils	Serum IGE	ACQ Score
Omalizumab												
Allergic asthma/asthma with elevated IgE												
Vignola 2004[99] SOLAR	405	12 to 75	Moderate to severe	N/A	≥12%	2 or more	High dose ICS	Excluded if OCS	N/A	N/A	≥30 to ≤1300 IU/ml	-
Humbert 2005[42] INNOVATE	419	12 to 75	Severe	≥40 to ≤80% predicted	≥12%	2 or more	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[44] ICATA	419	6 to 20	Severe	N/A	N/A	1 or more	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-
Hanania 2011[100]	850	12 to 75	Severe	≥40 to ≤80% predicted	NR	1 or more	High dose ICS and another controller	Maintenance permitted	NR	NR	>30 to <700 IU/ml	-
Bardelas 2012[101]	271	At least 12	Severe	≤80% predicted	NR	dx asthma at least 12 months	Medium dose ICS and another controller	No	N/A	N/A	>30 to <700 IU/ml	-
Busse 2013[39]	328	12 to 75	Severe	>80% predicted	N/A	1 or more	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Critera	Sputum Eosinophils	Serum IGE	ACQ Score
Li 2016[102]	616	18 to 75	Moderate to severe	≥40 to ≤80% predicted	≥12%	2 or more	Medium dose ICS and another controller	No	N/A	N/A	NR	-
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[43] DREAM	616	12 to 74	Severe		Improvement more than 12% with inhaled salmeterol or variability of more than 20% between clinic visits	2 or more	At least 880 mcg fluticasone with or without OCS	No	>300	3% or more	NR	NR
Ortega 2014[69] MENSA	576	12 to 82	Severe	<80% predicted for adults or <90% predicted for adolescents	>12%	2 or more	AT least 880 mcg fluticasone and another controller	No	>150 at screening or >300 in previous year	NR	NR	NR
Chupp 2017[73] MUSCA	551	At least 12	Severe	<80% predicted for adults or <90% predicted for adolescents	NR	2 or more	High does ICS and another controller	If on OCS, exacerbations requiring doubling	>150 at screening or >300 in previous year	NR	NR	NR
OCS-dependent severe eosinophilic asthma												

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Critera	Sputum Eosinophils	Serum IGE	ACQ Score
Bel 2014[47] SIRIUS	135	At least 12	Severe	NR	NR	NR	Ay least 880 mcg fluticasone and another controller	At least 6 months OCS; at least 40 mcg for age 12-17	>300 during 12 months before or <150 during optimization	NR	NR	NR
Reslizumab												
Castro 2015[70]	953	12 to 75	Moderate to severe	NR	≥12%	1 or more	At least 440 mcg fluticasone with or without another controller including OCS	Allowed	≥400	NR	NR	≥1.5
Benralizumab												
Bleecker 2016[36] SIROCCO	1205	12 to 75	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	2 or more	high dose ICS; med or high for age 12-17	No	NR	NR	NR	>1.5
Fitzgerald 2016[37] CALIMA	1306	12 to 75	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	2 or more	Medium (≥250 mcg) to high dose ICS (≥500 mcg) fluticasone with another controller	No	>300	NR	NR	NR
OCS-dependent severe eosinophilic asthma												

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Critera	Sputum Eosinophils	Serum IGE	ACQ Score
Nair 2017[48] ZONDA	220	Adults	OCS for at least 6 months	NR	NR	NR	NR	NR	≥150	NR	NR	NR
Dupilumab												
Wenzel 2016[103]	769	At least 18	Moderate to severe	≥40 to ≤80% predicted	≥12%	1 or more	At least 500 mcg fluticasone and at least one other controller	NR	NR	NR	NR	≥1.5
Castro 2018[38] LIBERTY ASTHMA QUEST	1902	At least 12	Moderate to severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	1 or more	At least 500 mcg fluticasone ad up to two other controllers	NR	No minimum	No minimum	NR	NR
OCS-dependent severe asthma												
Rabe 2018[49] LIBERTY ASTHMA VENTURE	210	At least 12	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	NR	At least 500 mcg fluticasone ad up to two other controllers	On OCS	No minimum	No minimum	N/A	NR

ACQ: Asthma Control Questionnaire, ICS: Inhaled corticosteroids, FEV1: Forced expiratory volume in 1 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[99] SOLAR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Humbert 2005[42] INNOVATE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2011[44] ICATA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Hanania 2011[100]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Bardelas 2012[101]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2013[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Li 2016[102] Chinese Omalizumab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[43] DREAM	Yes	Yes	Yes	Yes	Yes	16% withdrew	Yes	Yes	No	Yes	Yes	Good
Ortega 2014[69] 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[73] MUSCA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Bel 2014[47] SIRIUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Reslizumab												
Severe eosinophilic asthma												
Castro 2015[70]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Benralizumab												
Bleecker 2016[36] SIROCCO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Fitzgerald 2016[37] CALIMA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Nair 2017[48] ZONDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Dupilumab												
Moderate to severe uncontrolled asthma												
Wenzel 2016[103]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Castro 2018[38] 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[49] 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[99] 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[42] 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[44] 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[100]	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[101]	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[39]	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[102] 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[43] 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[69] 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
	Diffference 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[73] 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[47] 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[70]	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[36] 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[37] 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[48] 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[103]	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[38] 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							
Rabe 2018[49]	Dupilumab 300 mg	103	0.7	NR	NR	0.21	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
LIBERTY ASTHMA VENTURE	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[99] 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[42] 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[44] 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[100]	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[101]	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[39]	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[102] 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[43] 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[69] 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
	Diffference SC vs. Placebo	NR	-0.44 (-0.63 to -0.25)	NR	-7 (-10.2 to -3.8)	NR	NR	NR
Chupp 2017[73] 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[47] 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[70]	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[36] 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[37] 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[48] 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[103]	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[38] 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[49] 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 1 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[99]	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[42]	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[44]	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[100]	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[101]	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[39]	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[102]	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[43] 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[69]	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[73] 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[47] 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[70]	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[36]	Benrizliumab 30 mg q 4 weeks	293	73%	12%	<1%	NR	2%	3%	4%	7%	11%	4%
	Benrizliumab 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[37] CALIMA	Benrizliumab 30 mg q 4 weeks	425	74%	10%	<1%	12%	2%	3%	3%	8%	7%	5%
	Benrizliumab 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												
Nair 2017[48] ZONDA	Benralizumab 30 mg q 4 weeks	72	68%	10%	0%	NR	0%	1%	3%	7%	6%	7%

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
	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[103]	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[38] 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[49] 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 eosihophils (≥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 analysis was conducted using a random effects Bayesian framework with the gemtc package in R. Inputs used for the analysis are reported in Appendix Table D7.

Table D7: Network Meta-Analysis Data Inputs: Asthma Exacerbation Rates in Patients with ≥300 eosinophils/µL

Study	Intervention(s)	Exacerbation Rate (95% CI)	Rate ratio vs. Placebo (95% CI)
Busse 2013[39]	Placebo	0.59 (NR)	0.41 (0.20, 0.82)
	Omalizumab	0.25 (NR)	
EXTRA[104]	Placebo	1.03 (NR)	0.68 (0.52, 0.89)
	Omalizumab	0.70 (NR)	
Casale 2018[105]	Placebo	NR	0.33 (0.16, 0.64)
	Omalizumab	NR	
DREAM[40]	Placebo	1.65	0.73 (0.40, 1.33)
	Mepolizumab	1.21	
MENSA[40]	Placebo	1.98 (NR)	0.39 (0.28, 0.55)
	Mepolizumab	0.78 (NR)	
Study 1 (Castro 2015)[70]	Placebo	1.80 (NR)	0.50 (0.37, 0.67)
	Reslizumab	0.90 (NR)	
Study 2 (Castro 2015)[70]	Placebo	2.11 (NR)	0.41 (0.28, 0.59)
	Reslizumab	0.86 (NR)	
CALIMA[37]	Placebo	0.93 (0.77, 1.12)	0.72 (0.54, 0.95)
	Benralizumab	0.66 (0.54, 0.82)	
SIROCCO[36]	Placebo	1.33 (1.12, 1.58)	0.49 (0.37, 0.64)
	Benralizumab	0.65 (0.53, 0.80)	
LIBERTY ASTHMA QUEST[38]	Placebo 200mg	1.08 (0.85, 1.38)	0.34 (0.24, 0.48)
	Dupilumab 200mg	0.37 (0.29, 0.48)	
	Placebo 300mg	1.24 (0.97, 1.57)	0.33 (0.23, 0.45)
	Dupilumab 300mg	0.40 (0.32, 0.51)	
Wenzel 2016[103]	Placebo	1.04 (0.57, 1.90)	0.29 (0.11, 0.76)
	Dupilumab 200mg	0.30 (0.13, 0.68)	
	Dupilumab 300mg	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)

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.[106]

Lifetime Annualized Clinical Outcomes

Tables E.2 -E.6 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 E.2. 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)	0.30	0.031	-0.001

SoC: Standard of care

Table E.3. 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 E.4. 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 E.5. 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 E.6. Long-Run Clinical Outcomes: Dupilumab

Dupilumab: Average Events per Person Year			
Average Events per Person Year	**Dupilumab**	**SoC**	**Incremental**
Steroid Burst	0.623	1.141	-0.518
ED Visit	0.035	0.063	-0.029
Hospitalization	0.035	0.063	-0.029
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of care

Sensitivity Analysis Results

Tornado Diagrams not included within the Draft Report

Figure E.1. Omalizumab Tornado Diagram

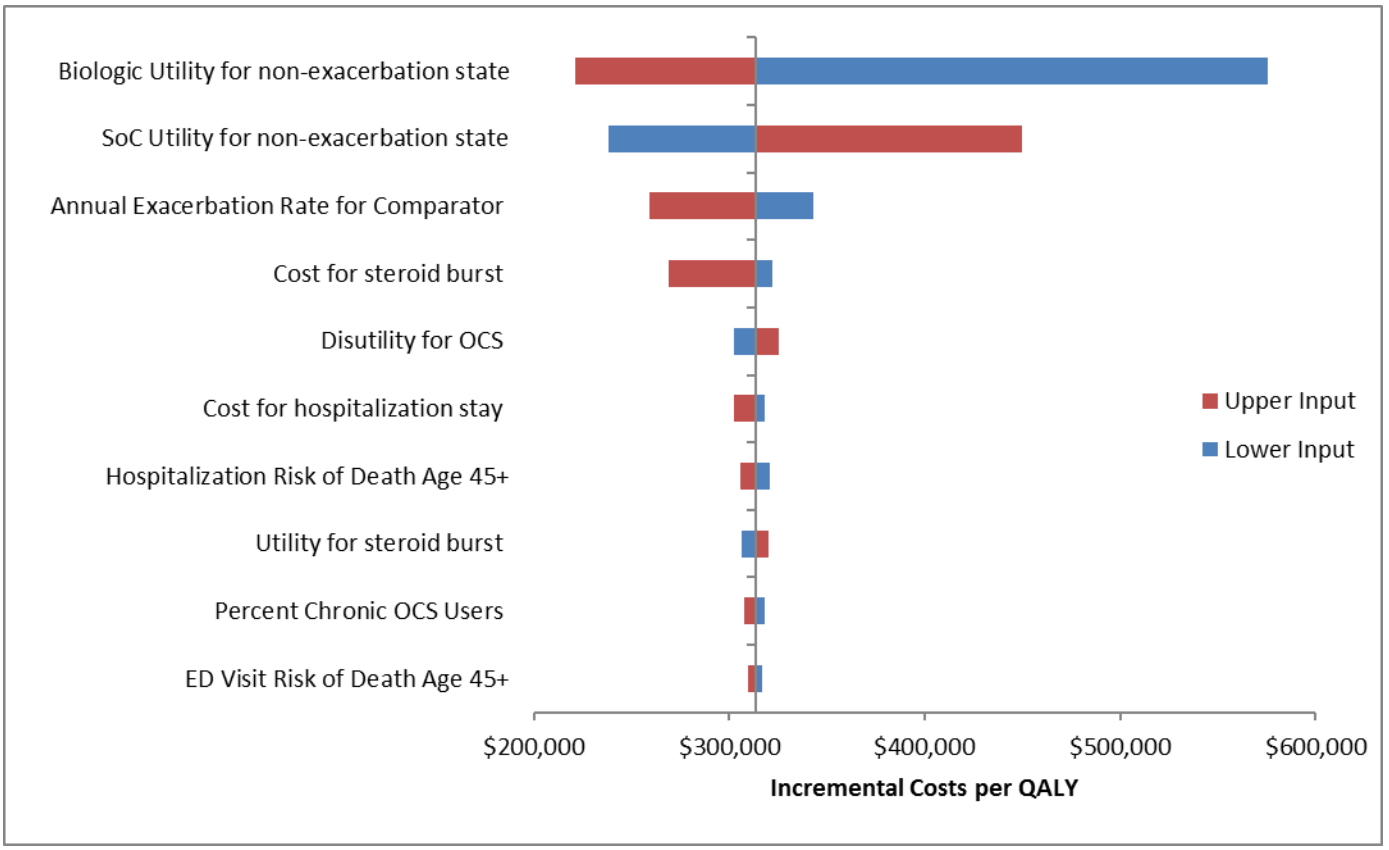


Figure E.2. Reslizumab Tornado Diagram

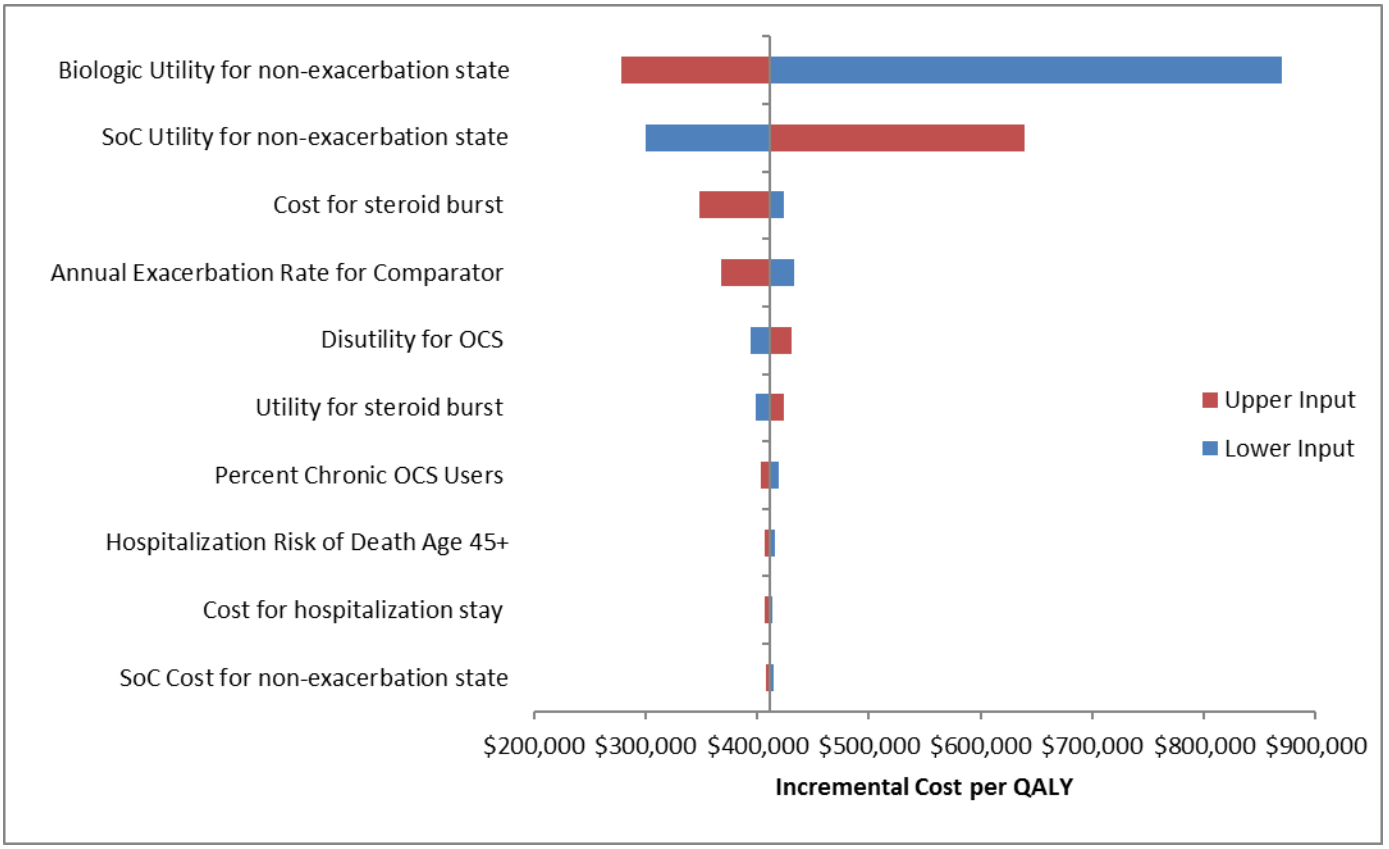


Figure E.3. Benralizumab Tornado Diagram

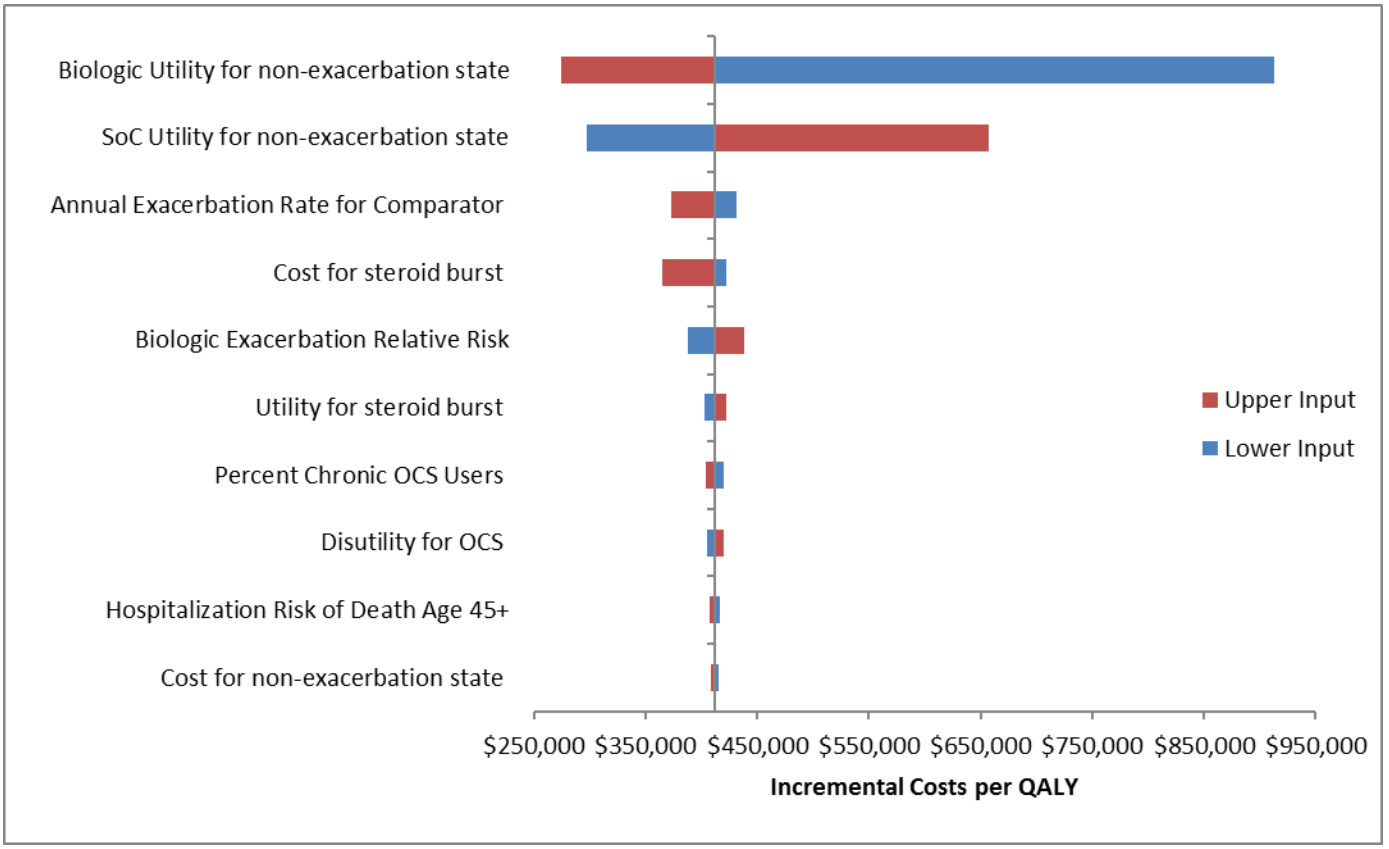


Figure E.4. Dupilumab Tornado Diagram