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

Final Background and Scope

June 13, 2018

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 direct medical costs of asthma are estimated to be $50 billion.[2] Individuals with severe asthma represent less than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids and long-acting beta agonist therapy, these patients are often treated with oral corticosteroids.[3] About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells, increased signaling in the IL-4, IL-5, and IL-13 pathways, and increased eosinophils in both the blood and airways.[4,5]

This assessment will consider 5 monoclonal antibodies that alter the pathways involved in the type 2 inflammatory phenotype of asthma. The drugs, dosing, their mechanism of action, and their FDA indications for asthma are summarized in Table 1 below.

Table 1: Monoclonal Antibody Therapies for Type 2 Inflammation in Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®)	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[6]
Mepolizumab (Nucala®, Glaxo Smith Kline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[7]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[8]
Benralizumab (Fasrena™, 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[9]
Dupilumab (Dupixent®, Regeneron/Sanofi)	300 mg SC Q 2 weeks	Anti-IL-4Rα	*PDUFA date 10/20/2018[10]

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

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of five biologic therapies for asthma: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

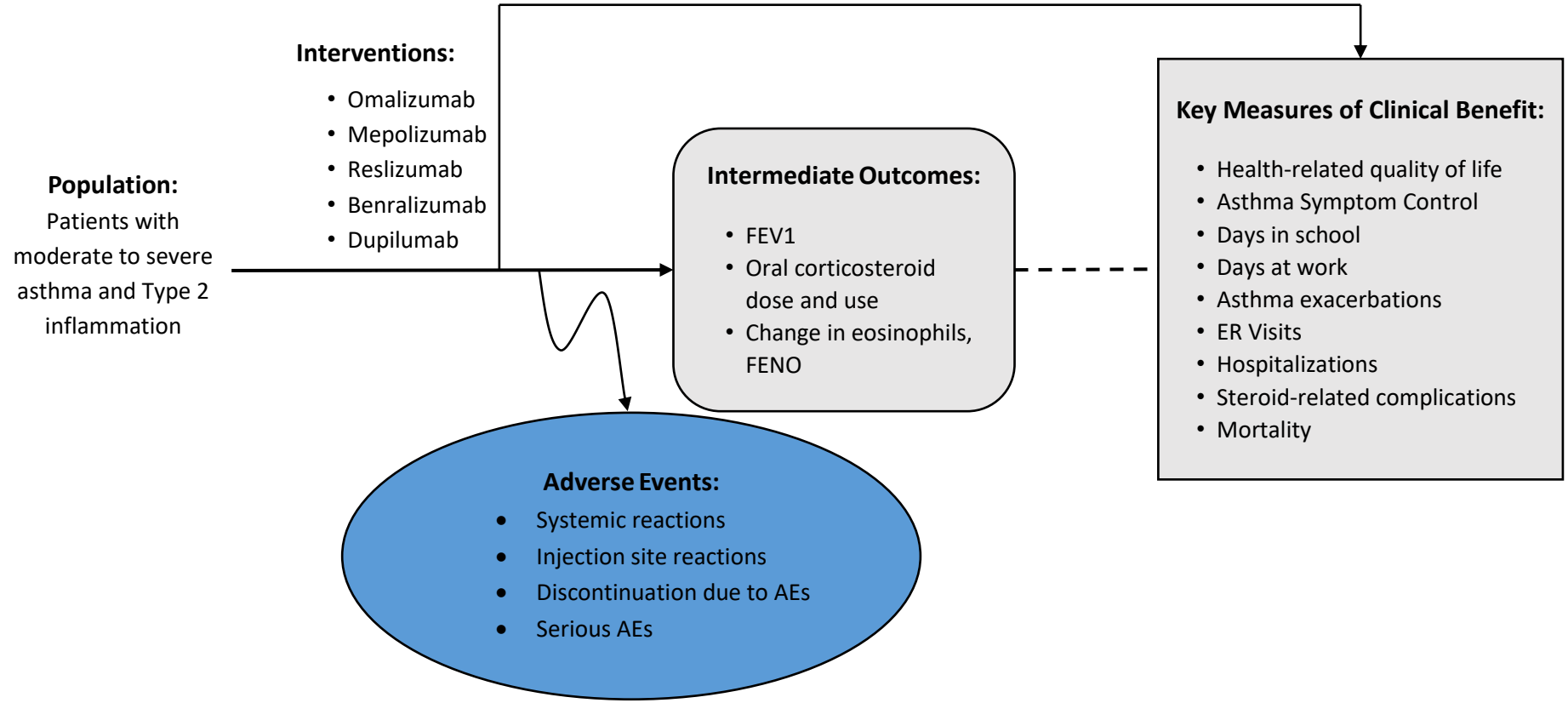
The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include 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/). All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope 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 on the following page.

Figure 1. Analytic Framework: Asthma Management with Biologic Therapies



Note: SAEs: severe adverse effects; AEs: adverse effects; FEV_1: forced expiratory volume in 1 second; FENO: fractional exhaled nitric oxide

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 ellipsis.[11]

Populations

The population of focus for the review will be adults and children ages 6 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. 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.[4,12] 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 will also focus on 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 2 or 4 weeks
- Mepolizumab 100 mg by subcutaneous injection once every 4 weeks
- Reslizumab 3 mg/kg by intravenous infusion once every 4 weeks
- Benralizumab 30 mg by subcutaneous injection once every 4 weeks x 3; then every 8 weeks
- Dupilumab 300 mg by subcutaneous injection once every 2 weeks

Comparators

The comparators of interest will be daily inhaled corticosteroids plus at least one additional controller therapy, or daily inhaled corticosteroids plus at least one additional controller therapy and one of the other biologics listed. We recognize that there may be insufficient data for direct or indirect comparisons between the five biologic agents that are under review.

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 (AQLQ)
- Asthma control assessed by standard questionnaires (ACQ or ACT)
- Asthma exacerbations
- 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 1 second (FEV_1)
- Absence from school
- Absence from work
- Adherence

Timing

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

Settings

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

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 2. 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 "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a decision analytic model to assess the cost-effectiveness of each intervention included in the clinical evidence review (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) added to standard of care (e.g. inhaled corticosteroid therapy and at least one additional controller medication), as compared to standard of care alone in patients with moderate-to-severe asthma. To assess the incremental costs per outcomes achieved, we will conduct a cost-effectiveness analysis from the health system perspective. A Markov model will track asthma-related outcomes and costs in a representative population for each of the interventions over a lifetime time horizon.

A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. The model structure will be based on a previously developed model assessing the cost-effectiveness of mepolizumab, which was based on a previously published long-term model of severe asthma.[13,14] The Markov model will simulate the target patient population through three primary health states: asthma non-exacerbation (i.e., day-to-day asthma symptoms), asthma exacerbation (including three mutually exclusive subcategories:

asthma-related events that requires an oral corticosteroid burst, asthma-related ED visits, or asthma-related hospitalizations), and death (including asthma-related mortality and other cause mortality). Key clinical inputs for the model, informed by the evidence review, will include exacerbations (including oral steroid bursts, emergency room visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, day-to-day asthma symptoms, asthma control and health-related quality of life. Probabilities, costs, and other inputs will differ to reflect varying effectiveness among interventions.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcomes of each intervention will be evaluated in terms of life years gained and quality-adjusted life years gained. Quality of life weights will be applied to each health state, including potential quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to the interventions and their administration, condition-related care including treatment of exacerbations, and serious adverse events. In addition, the perspective will be expanded to a societal one in a scenario analysis to incorporate other patient outcomes such as asthma-related productivity gains and losses. Pairwise comparisons between the interventions of interest will be performed if the clinical evidence review finds sufficient evidence on relevant outcomes that suggest clinical separation. The primary model outcome will be expressed in terms of the incremental cost per QALY gained and incremental cost per life-year gained. If data are available that accurately define response to treatment, then a responder analysis will be undertaken.

In separate analyses, we will explore the potential health system budgetary impact of dupilumab over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of the intervention.

More information on ICER's methods for estimating potential budget impact can be found at: https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include 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.

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