

Tezepelumab for Severe Asthma

Draft Background and Scope

May 6, 2021

Background

This draft scope incorporates information and language from prior ICER reviews of asthma in [2016](#) and [2018](#).

The Centers for Disease Control and Prevention (CDC) estimates that 25 million Americans have asthma of whom 5 million are children.¹ Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging of 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 10 million office visits, 1.6 million emergency room visits, 180,000 hospitalizations, and 3,500 deaths each year in the US.^{1,2} 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 In the US, asthma is more than twice as common among Black children as among white children (13.5% and 6.4%, respectively), and remains somewhat more common among Black adults.¹

Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).³

Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 (Th2) cells.⁴ These cells secrete interleukin (IL)-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.^{5,6} The ICER report in 2018 reviewed five monoclonal antibodies that primarily targeted pathways involved in the allergic or type 2 inflammatory phenotypes of asthma.

Tezepelumab is a new monoclonal antibody that targets thymic stromal lymphopoietin (TSLP); TSLP is believed to play important roles in type 2 immunity but, also in other inflammatory pathways.⁷ By targeting a new pathway, tezepelumab may provide a new option both for patients for whom prior monoclonal antibodies were indicated but did not work, and also for the large number of patients for whom existing monoclonal antibodies are not indicated. The US Food and Drug Administration granted breakthrough therapy designation to tezepelumab for the treatment of patients with severe asthma without an eosinophilic phenotype,⁸ and an FDA decision is expected near the end of 2021.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient groups, 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. A revised scoping document will be posted following a three-week public comment period. 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.

ICER, both for this report, and for prior reports, has heard from patients, patient groups, and clinicians about the need for treatments that allow patients to return to their usual activities of daily living. Symptom relief, asthma control, and quality of life matter much more to patients than a reduction in asthma exacerbations. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

We also heard about the excess burdens that asthma places on patients marginalized by society, both because of racism and because of economic inequality.

Report Aim

This project will evaluate the health and economic outcomes of tezepelumab for severe asthma. 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 on the following pages 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 ICER's [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 revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

The population of focus for the review is adults and adolescents with severe asthma. There are multiple definitions of moderate and severe asthma and some definitions have evolved over time. The Global Initiative for Asthma (GINA) defines severe asthma as a type of difficult-to-treat asthma that is 1) uncontrolled despite management of modifiable disease factors and despite adherence to maximally optimized high dose ICS-LABA treatment, or 2) asthma that worsens when high dose treatment is decreased.⁹ The European Respiratory Society (ERS)/American Thoracic Society (ATS) Management of Severe Asthma guideline defines severe asthma as asthma that requires or remains uncontrolled despite treatment with high dose ICS plus a second controller medication and/or OCS.

Apart from the subpopulations described below (related to indications for the comparator therapies), data permitting, we expect to examine efficacy in subgroups defined by:

- Allergic vs. non-allergic asthma phenotypes
- Eosinophil level
- Age

Interventions

The intervention of interest is tezepelumab (Amgen and AstraZeneca)

Comparators

The 2018 ICER asthma report found similar efficacy among the four biologics targeting type 2 asthma and the evidence was inadequate to distinguish their net health benefits. Among those therapies, dupilumab has a slightly broader indication that includes patients dependent on OCS. As such, we expect that comparison to dupilumab will be adequate to represent these four agents in this review. Omalizumab, an anti-IgE antibody has a different indicated population than dupilumab.

Data permitting, we intend to compare tezepelumab to:

- Dupilumab (Dupixent[®], Sanofi and Regeneron) in patients for whom dupilumab is indicated
- Omalizumab (Xolair[®], Genentech) in patients for whom omalizumab is indicated
- Usual care (estimated by placebo arms of clinical trials) in all patients with severe asthma

Outcomes

A multistakeholder project launched in 2019 concluded that a core set of outcomes that should be measured in trials of therapies for severe asthma includes severe asthma exacerbation, change in asthma control, asthma-specific or severe asthma-specific quality of life, asthma-specific hospital stay or admission, and asthma-specific emergency department visits.¹⁰

Although this core outcomes set was published after trials of the therapeutic agents subject to this review were conducted, the set helps inform outcomes that will be sought as part of this review.

The outcomes of interest are described in the list below:

- Patient-Important Outcomes
 - Daily quality of life
 - Daily symptoms (including nocturnal symptoms and impact on daily activities)
 - Asthma control
 - Asthma-related hospitalizations and emergency department visits
 - Use/reduction in use of OCS
 - Corticosteroid side effects
 - Asthma exacerbations
 - Missed time from school or work
 - Mortality
 - Adverse events including
 - Serious adverse events
 - Treatment-emergent adverse events
 - Adverse events leading to treatment discontinuation
- Other Outcomes
 - Pulmonary function testing including forced expiratory volume in 1 second (FEV1)
 - Adherence
 - Blood eosinophil levels

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, with a focus on outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

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

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients’ ability to achieve major life goals related to education, work, or family life
Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients’ ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

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 an economic model to assess the lifetime cost effectiveness of tezepelumab added to standard of care (e.g., inhaled corticosteroid therapy and at least one additional controller medication) relative to standard of care alone in patients with severe asthma. Data permitting, the other active comparators (omalizumab and dupilumab) added to standard of care will be compared to standard of care alone. The model structure will be based on a previously developed model from prior ICER reports, assessing the cost effectiveness of interventions in severe asthma.¹¹⁻¹³

The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per QALY, and/or when the result crosses the threshold of \$100,000-\$150,000 per QALY gained. The target population will consist of patients with severe asthma who are eligible for tezepelumab; comparator therapies will only be modeled in populations eligible to receive them.

The model will consist of health states including an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event requiring an OCS burst, asthma-related emergency department visit, or asthma-related hospitalization), and death (including asthma-exacerbation related mortality, asthma-related mortality, and all-cause mortality). Further, the model will be able to accommodate chronic OCS use for a proportion of the modeled cohort and a treatment's potential impact on reducing chronic OCS use. We will assess outcomes over a lifetime time horizon. The cycle length will use a 2-week cycle to represent the average duration of asthma exacerbations. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between 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 exacerbations avoided, % of patients who achieve treatment response, and other possible measures of quality of life improvement or symptom reductions, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained ([evLYG](#)). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. Utilities will be derived from generic health status instruments (e.g., EuroQoL 5-dimension [EQ-5D]) and/or disease-specific instruments (e.g., asthma quality of life questionnaire [AQLQ]) that have literature-based mapping functions to the EQ-5D. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. All costs will be inflated to 2021 US dollars. Results will be expressed in terms of the incremental cost per QALY gained, cost per evLYG, cost per life year gained, and cost per exacerbation avoided. If data permit, we will explore incremental outcomes using a responder evaluation and model subsequent active treatment for only those who respond. Additionally, data permitting, we will also explore potential scenario analyses around subgroups of patients (e.g., inner city residents) with higher baseline severity of asthma. Costs and outcomes will be discounted at 3% per year.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This potential budgetary impact analysis will highlight the relation between treatment prices and level of uptake for a given budget impact, and will allow

assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found [here](#).

Identification of Low-Value Services

ICER 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 ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by tezepelumab (e.g., reduction in exacerbations, ED 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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