



Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, Massachusetts 02109

October 14, 2021

Dear Dr. Pearson,

I am writing on behalf of the Asthma and Allergy Foundation of America (AAFA) to comment on your recent draft evidence report, “Tezepelumab for Severe Asthma,” which found that “tezepelumab reduces exacerbations in patients with severe asthma, including in some types of asthma for which other biologic therapies are not effective.”¹ We are encouraged by this finding and hopeful that this new monoclonal antibody might be effective for certain patients.

Concerns

Despite the overall positive conclusion about tezepelumab’s effectiveness, we are concerned that the draft report reflects inaccurate assumptions about potential use, undervaluing quality of life and overestimating potential uptake. As we noted in 2018 comments on ICER’s review of biologic therapies for asthma,² only a relatively small proportion of patients with moderate to severe asthma receive biologics, and typically only for a short duration. Furthermore, it is important not to underestimate the value of biologics that can address exacerbations that may lead to death.

ICER’s review also seems to understate the importance of the new possibilities tezepelumab raises for treatment. It appears likely that tezepelumab will not have a phenotype restriction, making it effective for asthma with either allergic or eosinophilic phenotypes, or mixed phenotypes. It would also be the only biologic therapy for T2-low asthma (i.e. non-allergic and

¹ Tezepelumab for Severe Asthma, Draft Evidence Report, Institute for Clinical and Economic Review, at ES2.

² AAFA letter to ICER on Draft Report “Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation” (Oct. 22, 2018). <https://www.aafa.org/media/2398/aafa-comment-letter-icer-draft-report-biologic-therapies.pdf>



non-eosinophilic). AAFA considers the emergence of treatments for patients with no similar options to be particularly important for our community.

AAFA is also concerned that the draft report seems to reach a conclusion regarding cost effectiveness of the product despite unknown pricing information. The report acknowledges that “[p]ricing for tezepelumab is not yet known but at anticipated prices the treatment will not reach traditional thresholds considered cost-effective in the US market.”³ Basing this conclusion on “anticipated prices” is premature. As we stated regarding ICER’s review of peanut allergy treatments in 2019,^{4,5} conducting a review prematurely risks limiting access – or creating fears about limited access among people who could potentially benefit from this drug – when adequate information is not yet available. We urge caution in this area until additional information about pricing can be determined and analyzed.

We also recommend that ICER modify the Questions for Deliberation and Voting so “yes” and “no” are not the only responses available for a committee vote. Given the early review of this therapy by ICER but before FDA review and long-term data availability, ICER should reflect this nuance in the voting questions for example by adding “NA” for not applicable or another selection that does not force the committee into binary voting choices.

Moving toward reflecting equity in ICER analyses

We do appreciate that, consistent with our earlier recommendation, the draft report notes that most clinical trials, including those for asthma drugs, disproportionately enroll white participants, even though asthma is more prevalent and has more serious effects among Black Americans and other ethnic minority groups. We encourage ICER in future reports and analysis to continue to, at a minimum, strive to detail the representativeness, or lack thereof, of clinical trial data, and discuss how any lack of representation may impact the analysis.

³ *Id* at ES3.

⁴ AAFA statement, “Asthma and Allergy Foundation of America Elevates Patient Voice in ICER Review of New Peanut Allergy Treatments” (June 14, 2019). <https://www.aafa.org/media/2436/aafa-letter-icer-review-treatments-peanut-allergy.pdf>

⁵ AAFA statement, “Asthma and Allergy Foundation of America Responds to Premature ICER Review of New Peanut Allergy Treatments” (July 11, 2019). <https://www.aafa.org/media/2439/aafa-statement-on-icer-final-report-for-peanut-allergy-therapies.pdf>



The draft also makes clear that a treatment that benefits people with asthma will be particularly impactful for those minority populations that are most impacted. As noted in our earlier correspondence with ICER, AAFA is deeply concerned about racial and ethnic disparities in asthma, rooted in a broad range of social determinants that affect individual and community risk.⁶ The most affected communities are, in many ways, most in need of effective treatments, and we urge ICER to continue to note where such impacts may occur.

Conclusion

Our goal is for all patients with asthma to be able to access the medication they need, through reasonable pricing and adequate insurance coverage. We look forward to continuing to provide input on ICER's work in this area. Thank you for your time and attention.

Sincerely,

Kenneth Mendez
President & CEO
Asthma and Allergy Foundation of America

⁶ Asthma and Allergy Foundation of America, "Asthma Disparities in America" (2020). Available at <https://www.aafa.org/asthma-disparities-burden-on-minorities.aspx#pdf>



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September 24, 2021

PUBLIC COMMENT FOR REVIEW OF SEVERE ASTHMA TREATMENT

As President of the American Association for Respiratory Care (AARC), I am writing to express concerns over the potential for the Institute for Clinical and Economic Review (ICER) to limit access to *tezepelumab*, the first biologic to have shown consistent and significant reductions in exacerbations in a broad population of severe asthma patients.

The AARC is a national professional organization of 40,000 members and whose organizational activities impact over 190,000 practicing respiratory therapists across the country. Respiratory therapists are medical professionals who specialize in all aspects of pulmonary medicine and treat patients who suffer from chronic respiratory conditions like chronic obstructive pulmonary disease (COPD), asthma, pneumonia, lung trauma and other respiratory-related diagnoses such as COVID-19.

Tezepelumab has been granted Priority Review by the U.S. Food and Drug Administration. because it believes the biologic, if approved, would offer significant improvements in the safety or effectiveness for the treatment of severe asthma when compared to standard applications. Of concern to the AARC, and respiratory therapists who treat the disease, is the fact that patients with severe asthma are commonly prescribed the same treatment modalities as those who suffer mild or moderate asthma, although severe asthma imposes more life-threatening symptoms. That is why unfettered access to this new and promising biologic is mandatory for patients with severe asthma who face twice the risk of emergency visits to the hospital and an increased risk of mortality.

It is also important to note that asthma compounds health disparities, especially among Black Americans and those living below poverty levels and exposed to environmental triggers. Access to a new biologic with promising results of significant improvements over current treatments offers the option to give patients of all backgrounds and races a better chance of managing severe asthma.

As we understand the process, ICER uses a “health economics” approach in determining whether a new drug is worth the cost. While clinical trials data and available pricing information are taken into consideration, we are concerned that an analysis that relies too heavily on quantitative data does not account for the quality of life that matters most to patients, such as the ability to work, attend social functions, and enjoy time with family and friends. Treatment modalities can’t be a “one size fits all” compromise. People living with severe asthma, along with their

family and caregivers, are daily burdened, even frightened, by the persistent and often unpredictable impact of symptoms.

ICER has a chance to make a difference and provide clinicians and patients suffering from severe asthma a new targeted treatment that could provide unprecedented relief and an improved quality of life. Because each patient's experience with severe asthma is not exacerbated by the same triggers, different drugs offer different benefits. Now is the time to give those patients with severe asthma a chance for a new, promising treatment that can make a difference in their lives.

Sincerely,

A handwritten signature in cursive script that reads "Sheri Tooley". The signature is written in black ink and is positioned below the word "Sincerely,".

Sheri Tooley BSRT, RRT, RRT-NPS, AE-C, CPFT, FAARC
President and CEO 2021-2022



October 14, 2021

The American College of Allergy, Asthma, and Immunology appreciates the opportunity to review and comment on the Draft Evidence Report for the Severe Asthma Review of tezepelumab by ICER. The report was reviewed by members of our Asthma and Biologics Committees that are clinicians, both academic and practicing allergists/immunologists, who provide medical care for patients with asthma throughout the United States. We have several concerns with the draft report.

First and foremost, since tezepelumab has not been approved by the FDA, we do not believe that the cost assumptions are valid, nor is it possible to compare to other biologics given differences in protocol design and lack of long-term efficacy and safety for tezepelumab. Furthermore, the FDA requires that measures of exacerbation reduction be included in the clinical trials which ICER apparently feels is not an accurate measure. We feel this review, prior to FDA approval, is premature, as we need to gain experience with tezepelumab before these kinds of documents are produced and endorsed by organizations.

We are also very concerned about the way information is presented regarding comparing the efficacy of tezepelumab to dupilumab or omalizumab. Without a head-to-head comparison study, this presented summary remains speculative and hypothetical. Rather than drawing hypothetical comparisons, it may be more suitable to present the data supporting the efficacy and safety of tezepelumab and highlight examples from the cost-impact of the previously FDA-approved biologics.

Finally, we are very concerned with the continued use of the quality-adjusted life year (QALY) and the Equal Value of Life Years Gained (evLYG) in commenting on a treatment prior to approval by the FDA and availability for use of the drug for a larger population outside of the clinical trials. Asthma is a complex, multifaceted disease with multiple phenotypes that leads to significant impact on quality of life and morbidity and mortality, especially among disadvantaged populations. We are aware that ICER is aware that these measures may lead to inappropriate application by policymakers (third-party payers) and urge that the “Safeguard Language to Ensure the Ethical and Appropriate Use of QALY-Based Analysis” be highlighted in the final document.

Sincerely,

Luz S. Fonacier, MD, FAAAAI
President
American College of Allergy, Asthma
and Immunology

James M. Tracy, DO, FAAAAI
Chair
Advocacy Council of ACAA

SUMMARY

Amgen and AstraZeneca appreciate the opportunity to comment on ICER's *Severe Asthma Draft Evidence Report for Tezepelumab*. Severe, uncontrolled asthma affects only 5-10% of total asthma patients, yet accounts for 50% of direct healthcare costs, and causes significant mortality and morbidity compared to non-severe asthma.^{1,2,3,4,5,6} Severe, uncontrolled asthma often results in patients ending up in the emergency room (ER) or hospital. It further contributes to a substantial loss in quality of life for patients, with ongoing symptoms and exacerbations despite the use of high-dose inhaled corticosteroids (ICS) and an additional controller such as long-acting beta-agonists (LABA).^{7,8} Tezepelumab is a potential first-in-class medicine with the ability to transform treatment for patients with severe asthma regardless of their type of inflammation, including those with/without eosinophilic or allergic phenotypes.^{9,10,11,12}

Amgen and AstraZeneca are committed to helping patients living with severe asthma. We highlight important recommendations below for ICER's Draft Evidence Report to reflect a more accurate and fair-balanced assessment:

1. The draft report overestimates the budget impact from adding tezepelumab, which could inappropriately signal access restrictions for patients.

We request ICER:

- revise the prevalence of severe uncontrolled asthma patients to align with published estimates (which is lower than what is reflected in the draft report), and
- include the use of other biologics to better reflect current utilization of asthma biologics in the US (biologic-eligible patients are overestimated in the draft report).

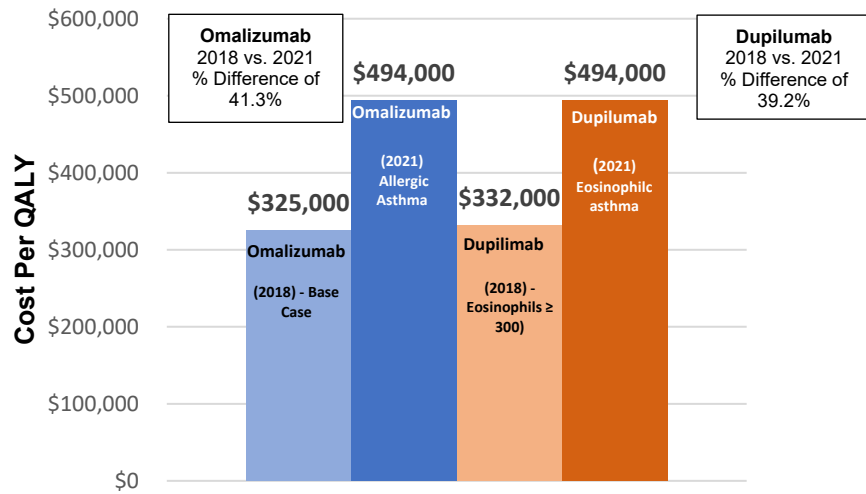
2. The draft report underestimates the risk of death in the calculation of the mortality risk per hospitalization, which inaccurately suggests a lower cost-effectiveness of tezepelumab and limits the external validity of the model.

- We request ICER update the mortality risk per hospitalization to align with observed severe asthma patients' death rates (which is higher than what is assumed in the model).

The next sections expand on our recommendations and present additional considerations.

In addition, it is important to note there is an overall inconsistency in the results from ICER's previous 2018 severe asthma assessment vs. the 2021 assessment.^{13,14} ICER's modified approach has resulted in a 39.2% to 41.3% difference in the cost per QALY (see Figure 1 below).

Figure 1: Comparison of the Cost-Effectiveness Ratios from ICER’s 2018 Severe Asthma vs.2021 Severe Asthma Assessment.



KEY RECOMMENDATIONS

1. Budget Impact: The draft report overestimates the budget impact from adding tezepelumab, which could inappropriately signal access restrictions for patients.

- We request ICER revise the prevalence of severe uncontrolled asthma patients to align with published estimates (which is lower than what is reflected in the draft report).

The proportion of severe asthma patients with uncontrolled disease in ICER’s analysis is above the range of estimates in published literature. The CDC estimates the prevalence of asthma at approximately 22.5 million individuals 12 years of age and older,¹⁵ where (as referred to above) an estimated 5%^{16,17} of adolescents and 10%^{18,19} of adults, have severe asthma (2.1 million individuals). Published estimates of the proportion of severe asthma patients with uncontrolled disease range from 19.9% (≥2 exacerbations in a year) to 49.2% (based on asthma control test).²⁰ ICER applies 60%,²¹ which is the proportion uncontrolled by patient report for all asthma patients, based on a patient survey regarding daytime/nighttime symptoms and short-acting β-agonist (SABA) use, not exacerbation frequency.^{22,23} The vast majority of these patients were non-severe and were not receiving the intensive medication regimen used to treat severe asthma. ICER should revise the analysis, applying published estimates of the proportion of severe asthma patients in the US who are uncontrolled.

- We request ICER include the use of other biologics to better reflect current utilization of asthma biologics in the US (biologic-eligible patients are overestimated in the draft report).

The draft budget impact analysis does not reflect the current utilization of asthma biologics in the US. In ICER’s 2018 Asthma Assessment budget impact analysis, ICER

estimated 27% of patients with moderate to severe asthma were on biologics while 73% of the target population were on SoC alone.²⁴ Most (approximately 85%) severe uncontrolled asthma patients are already eligible for one or more of the currently available biologic therapies.²⁵ Approximately 15% of severe uncontrolled asthma patients are not eligible for current biologics.²⁶ As a result, tezepelumab will likely minimally increase the total number of patients receiving biologic therapy. Hence, it is clearly inaccurate to assume that in a world without tezepelumab, physicians would be treating all severe asthma patients with SoC alone. In the real-world study, CHRONICLE,²⁷ of the 1,428 eligible patients screened for enrollment, 57% of all biologic-eligible patients were receiving biologics. The breakdown of these biologics was as follows: 50% omalizumab, 28% mepolizumab, 23% benralizumab, 8% dupilumab, and 4% reslizumab.

2. *Mortality Risks: The draft report underestimates the risk of death in the calculation of the mortality risk per hospitalization, which inaccurately suggests a lower cost-effectiveness of tezepelumab and limits the external validity of the model.*

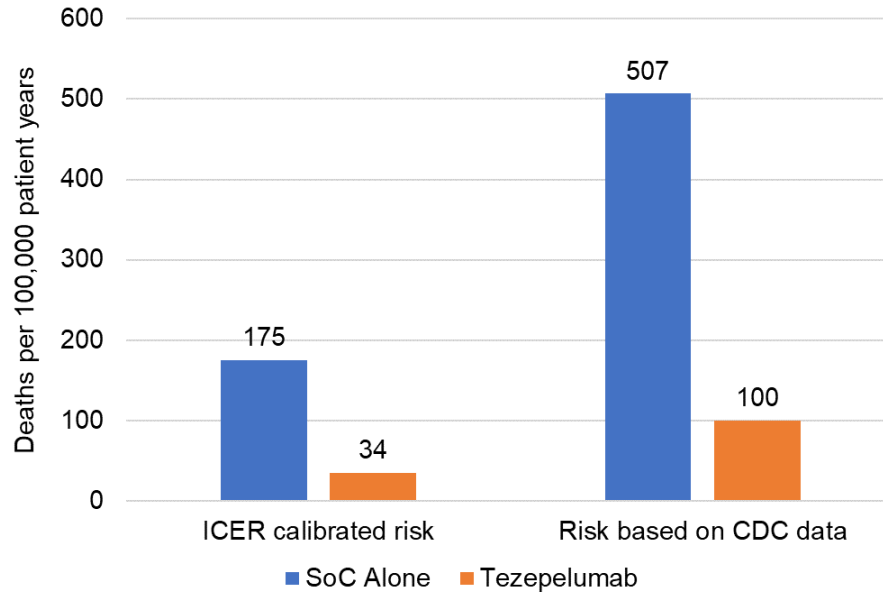
- We request ICER update the mortality risk per hospitalization to align with observed severe asthma patients' death rates (which is higher than what is assumed in the model).

ICER's calculation of the mortality risk per hospitalization underestimates the risk of death in the model. The value used in the model is 0.0068, which is lower than observed severe asthma patients' death rates. ICER should utilize CDC 2018 and 2019 data to recalibrate the model. The CDC reported 178,530 hospitalizations with a primary discharge diagnosis of asthma in 2018.²⁸ Combined with the 3,524 primary asthma deaths reported in 2019,²⁹ this suggests a risk of death per hospitalization of 0.01974.

Figure 2 below shows a 3-fold underestimation between the number of deaths predicted using ICER's calibrated death risk and the rate calculated above based on CDC reported hospitalizations, using the exacerbation and hospitalization rates from the model.

This is a critical variable that ICER's model is extremely sensitive to: the range of parameter values tested by ICER in sensitivity analyses does not capture the uncertainty in this model input, as it ignores the alternative values available in the published literature and other economic models of severe asthma. Underestimating these events limits ICER's cost-effectiveness model's external validity.

Figure 2: Predicted asthma deaths per 100,000 patient-years, comparison of ICER risk and risk based on CDC figures.



ICER’s model applies mortality risks only to exacerbations requiring hospitalizations.

The Draft Evidence Report states that, “consistent with NICE analyses, we assumed that all asthma-related deaths occur from severe exacerbations.” The 2021 Global Initiative for Asthma (GINA) guidelines defines severe exacerbations as exacerbations requiring emergency department (ED) attendance, hospitalization or a course of oral corticosteroid (OCS)³⁰ and additionally added a lung function criterion of peak expiratory flow (PEF) or forced expiratory volume (FEV₁) <60%.³¹ Furthermore, ICER’s approach does not align with NICE’s complete benralizumab appraisal.³² NICE’s approach for severe asthma incorporates several factors for severe exacerbation mortality risk from OCS burst to hospitalizations. Furthermore, all of NICE’s assessments of asthma biologics to date have included the risk of death for patients experiencing exacerbations with OCS burst or emergency room visits.^{33,34,35} The key difference is that ICER defines severe exacerbation as an “Asthma related event that requires a hospitalization”³⁶ vs. NICE’s approach, which more broadly defines severe exacerbation as “episodes in which patients require OCS for at least three days, an A&E visit or hospitalization, and have been shown to correlate with higher FeNO and a decrease in lung function”.³⁷

US CDC 2015-2019 death certificate data reported that a third of all asthma-related deaths occur outside medical facilities.³⁸ It is incorrect to assume that all asthma-related deaths occur within ER or hospital settings. The 2014 UK Royal College of Physicians National Review of Asthma Deaths supports this observation, estimating that 45% of asthma deaths (as concluded by an expert panel) in 2012-2013 (N=195) occurred before the individual could receive medical care.³⁹ Excluding fatalities that occur outside of medical facilities misses substantial health inequities for example, in distance to health care facilities (e.g., rural versus urban areas) and heterogeneity in the timing and quality of care. This is compounded in populations which may also disproportionately suffer from asthma (e.g., LatinX and Black populations).^{40,41,42,43,44,45}

ADDITIONAL CONSIDERATIONS

3. **Voting Questions:** We suggest ICER include a clarifying addition to voting question 5 (please add the **bolded** text below).

ICER Draft Voting Questions Page 2, Contextual Considerations: *“When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for severe asthma, on the basis of the following contextual considerations: 1= Very low priority; 2 = Low priority; 3 = Average priority; 4 = High priority; 5= Very high priority*

Voting Question 5: *Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability.*

- We suggest the following addition to the wording to voting question 5: ***“(i.e., ability to reduce potentially life-threatening exacerbations such as those leading to ER care/hospitalization).”***
4. **Early Insights Webinar:** In terms of ICER’s assessment process, we recommend going forward that ICER hold any early insights webinars after the comment submission, following the availability of the *Revised Report* to enrich the presentation with diverse perspectives.

CONCLUSION

Asthma is a heterogeneous disease with an enormous impact, burdening millions of people worldwide and placing massive pressure on healthcare systems globally. To enable a more accurate, fair-balanced assessment, we recommend that ICER adjust the budget impact analysis by re-estimating the US biologic-eligible severe uncontrolled asthma population per published estimates. Furthermore, we suggest that ICER revise the asthma-related mortality-related calibration by applying an alternative calibration for tezepelumab + SoC per observed data. These adjustments will help ICER achieve a more comprehensive assessment that seeks to accurately reflect the core values central to all stakeholders.

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October 14, 2021

Institute for Clinical and Economic Review

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

Dear ICER:

On behalf of the members of the American Thoracic
Society, I appreciate the opportunity to submit comments
on the recent ICER document: **Tezepelumab for Severe
Asthma Draft Evidence Report.**

As background, the ATS is a medical professional society
of over 16,000 members dedicated to prevention,
detection, treatment, cure, and research of pulmonary
disease, critical care illness, and sleep-disordered
breathing. The care and treatment of patients with asthma
is a high priority issue for the membership and leadership
of the ATS. It is with our great interest in asthma and
expertise that we offer the following key findings;

1. The report includes the relevant published clinical
trials of tezepelumab for the treatment of asthma.
2. The decision to compare tezepelumab to the
comparator dupilumab as representative of the four
currently approved treatments for eosinophilic asthma
(dupilumab, mepolizumab, benralizumab, and
reslizumab) is reasonable, as these agents have had
similar clinical benefits in phase III clinical trials.
3. The clinical benefit of Tezepelumab for the treatment
of patients with severe asthma is likely greater than the
ICER report recognizes. We note there are very few safe
and effective treatments for patients with severe asthma.
We further note that data from PATHWAY published
separately that looks at the proportion of patients that
had significant improvements (above the MCID) in ACQ
and AQLQ, which showed that 12% and 13% more
patients had significant improvements in ACQ and AQLQ

respectively compared to placebo. This provides more patient relevant data and counteracts the statement in the ICER report that “improvement in daily symptoms and quality of life are relatively small” ([10.1016/j.anai.2020.10.008](https://doi.org/10.1016/j.anai.2020.10.008))

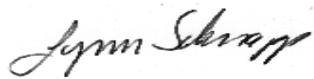
4. Patient and Caregiver Perspective section includes statements that the ATS believes should be revised. Section 2 on “Patient and Caregiver Perspectives” contains the sentence “Symptom relief, asthma control, and quality of life matter much more to patients than a reduction in asthma exacerbations.” This is a problematic statement that is not logical in the framework of the NIH asthma guidelines. Asthma control has two domains: reduction of impairment (reduction of symptoms and of ongoing need for rescue treatments; maintaining normal activity levels) and reduction of risk (prevention of exacerbations, acute health care utilization; minimization of medication side effects). “Asthma control” cannot be separated from prevention of asthma exacerbations. The ICER report to some extent seems to downplay the importance of preventing asthma exacerbations. Based on ATS asthma experts experience with patients, patients care a great deal about preventing asthma exacerbations, which are frightening, dangerous, require prednisone with its side effects, lead to ER visits, lead to missing work or childcare challenges, etc. We further note that for patients with severe asthma, exacerbations are likely more severe, more expensive and last longer than exacerbations experienced by patients with mild or moderate asthma. CER’s executive summary statement “Additionally, as with other biologic therapies, improvements in daily symptoms and quality of life are relatively small” downplays the benefit that biologics provide to some patients with severe asthma.
5. ICER should adjust the Tezepelumab rating. ICER rates the net health benefit of tezepelumab added to standard of care (SOC) versus SOC alone as C++. The ATS disagrees and recommends ICER change the rating to B+. The PATHWAY and NAVIGATOR trials show that tezepelumab + SOC is clearly superior to SOC alone in preventing asthma exacerbations. This is either a B or an A, depending on how much one values the prevention of asthma exacerbations. If one splits the difference, it’s a B+. We note, per figure 3.1, a C++ rating encompasses “comparable net benefit.” The PATHWAY and NAVIGATOR trials exclude the possibility – with 95% certainty – of a comparable net benefit between tezepelumab+SOC and SOC alone. None of the C ratings are compatible with the evidence.
6. The economic analyses appear to be thoughtful and rigorous, but they do not recognize the clinical reality that some patients with severe asthma experience clinical benefit from a particular biologic therapy while others do not, even though they may have similar clinical features. If a patient does not improve after 3-6 months on one agent, physicians often switch the patient to a different asthma biologic agent. If none of the biologics result in observed benefits, the use of biologics is discontinued. With this “trial and error” approach, clinicians attempt to find the right therapy that works for a specific patient. It does not appear that

the analysis of incremental costs over the “lifetime” time horizon accounts for the possibility that MDs may do a good job at tailoring therapy by “trial and error” such that patients incurring the lifetime incremental cost are fewer in number than the models predict and potentially are receiving greater benefits than the models predict. Importantly, Tezepelumab appears to provide somewhat broader efficacy than the previous biologics based on biomarker criteria. Thus, it is likely that there may be fewer “mistakes” made on initial prescribing.

7. The discussion in Uncertainties and Controversies may understate the effectiveness of biologics for the treatment of severe asthma. Biologics for the treatment of asthma, with their simpler regimens, may have an advantage with many patients who for complex systemic reasons have difficulty accessing routine care or adhering to complicated daily multi-drug regimens. As the report mentions, the results from these clinical trials may not be generalizable to routine practice but would be expected to have even greater benefits in routine practice where adherence and follow up frequency is more realistic.

The ATS appreciates the opportunity to comment on this report and hopes our comments will help improve the final ICER report. If you have questions about our comments or need additional information, please contact Mr. Gary Ewart (gewart@thoracic.org) in the ATS Washington Office.

Sincerely,



Lynn Schnapp MD ATSF

October 13, 2021

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft evidence report for severe asthma therapy tezepelumab

Dear Dr. Pearson:

Thank you for the opportunity to provide comments regarding ICER's *Draft Evidence Report on Tezepelumab for Severe Asthma*.

As a pulmonologist practicing in Pennsylvania, I treat patients with a wide range of respiratory illnesses, including asthma. I am board certified in pulmonary, critical care, and sleep medicine and am actively involved in many national and regional organizations including the American Thoracic Society, American College of Chest Physicians, American Association of Respiratory Care, and the American Association of Cardiovascular and Pulmonary Rehabilitation.

Over my career I have experienced many great improvements in the management algorithm for patients with asthma and in particular those with severe asthma. Early in my career I cared for many patients with uncontrolled asthma in the ICU setting who presented with an exacerbation. Over the last decade, I have seen very few (if any) patients admitted to the ICU with exacerbations. I think this can be attributed to the improvement in therapeutics over the last four decades. As such, I know firsthand the importance of new, innovative treatment options for severe, uncontrolled asthma.

As a physician, I can say firsthand that there is no "one-size-fits-all" treatment for asthma. Several innovative treatments have been approved in recent years that support patients living with severe asthma, but unfortunately there are still many patients that have yet to discover a treatment to control their symptoms. Tezepelumab may offer hope of successful disease management to many patients – but only if patients have the ability to access it. It truly should be the decision of the prescriber and the patient on what treatment regimen they wish to pursue, and we urge you to consider the value that new treatments provide.

I also ask you consider that ICER's reliance on the QALY is of great concern, especially when being used in an evaluation regarding asthma patients. As asthma is a chronic disease, the quality of life of patients, as defined by the QALY, is already diminished. This will lead to lower scores, even for drugs that are clinically effective, as patients with chronic diseases often cannot achieve perfect health.

The CDC estimates that 25 million Americans are living with asthma. Up to 2.5 million of those patients could be living with severe asthma. For these populations,

access to treatments is paramount. Patients with uncontrolled asthma continue to deal with frequent exacerbations, trouble sleeping, missed school/work, and emergency department visits. Not only can these negatively affect personal well-being, but there is a significant societal cost as well, with asthma care costing the US almost \$82 billion per year.¹ Effective treatments would serve to lower those societal costs.

I thank you for the opportunity and urge you to consider my comments. Should I be of any assistance, please contact me at bwcmd@yahoo.com.

Sincerely,

Brian W. Carlin, MD, FCCP, FAARC, MAACVPR
Sleep Medicine and Lung Health Consultants
Pittsburgh, PA

¹ <https://www.thoracic.org/about/newsroom/press-releases/journal/2018/asthma-costs-the-us-economy-more-than-80-billion-per-year.php>



October 14th, 2021

Institute for Clinical and Economic Review (ICER)
14 Beacon St Suite 800,
Boston, MA 02108

Dear ICER Review Panel:

Genentech, Inc. and Novartis Pharmaceuticals Corporation appreciate the opportunity to provide feedback on ICER's draft evidence report for "Tezepelumab for Severe Asthma: Effectiveness and Value." It is important to preserve access to multiple therapeutic options for patients with asthma, as it is a heterogeneous and chronic condition. Given our focus on applying excellent science and experience in allergic and inflammatory conditions, we offer the following recommendations to enhance the accuracy and interpretability of the report for healthcare decision-making:

- 1. Include an additional set of scenario analyses for all asthma populations (severe, eosinophilic, and allergic) using key model inputs from the 2018 ICER economic analyses.**
- 2. Remove statements regarding incremental clinical benefits between asthma biologics from the ICER report given the absence of comparative clinical effectiveness evidence.**
- 3. Update the clinical efficacy input for Xolair's exacerbations resulting in emergency department (ED) visits (without hospitalization) in the allergic asthma scenario analysis.**
- 4. Acknowledge Xolair's published clinical evidence among underserved racial and ethnic minority subgroups when discussing underrepresentation issues in clinical trials.**

We further expand on these recommendations with supporting rationale and implications below:

1. Include an additional set of scenario analyses for all asthma populations (severe, eosinophilic, and allergic) using key model inputs from the 2018 ICER economic analyses.

Specifically, for the additional scenario analyses, use the following alternative model inputs to align with the 2018 cost-effectiveness (CE) model [1]:

1. Utility value of 0.830 (0.020) for asthma without exacerbation based on the St. George's Respiratory Questionnaire (SGRQ) for all asthma biologics and 0.768 (0.015) for standard of care
2. Mean age of 46 years at treatment initiation
3. Distribution of exacerbations by type set to: 90% resulting in steroid burst, 5% resulting in ED visits, and 5% resulting in hospitalization
4. Risk of asthma-related mortality for exacerbations leading to hospitalization (2.48% fatal) and ED visits (1.79% fatal)
5. Annualized asthma exacerbation rate (AAER) of 1.30 per-person per year

Rationale: ICER performed multiple assessments of asthma biologics over the years using different model inputs and assumptions across reviews, based on the evidence for approved and new asthma biologics [1-3]. For example, in the 2016 and 2018 assessments, utility estimates for patients with asthma without exacerbations were consistent for all asthma biologics and were derived from the SGRQ, based on mepolizumab trial data (i.e., at 0.062 higher utility in the non-exacerbation health state compared to standard of care alone) [1, 3]. The 2021 assessment deviates from the past approaches to estimate unique on-treatment exacerbation-free utility estimates for each biologic using data from a different questionnaire, the Asthma Quality of Life Questionnaire [2]. ICER acknowledges that the utility estimate was the most influential driver of model results, as highlighted in the one-way sensitivity analyses. Further, most asthma biologics have a range of estimates for health-related quality of life impacts across randomized controlled trials, real world data, and questionnaires. Indeed, ICER has discussed this variation in utility estimates and their notable impact on CE model results in both the 2018 and 2021 draft report [1, 2]. Other important differences in key input assumptions between the 2021 and 2018 assessments include: a reduction in asthma-related mortality for severe exacerbations with an ED visit or hospitalization, a higher baseline exacerbation rate before treatment, a higher likelihood of ED visits and inpatient treatment for exacerbations, and higher mean age at the model start.

Moreover, the current 2021 review includes only two of the five available asthma biologics currently on the market (Xolair for allergic asthma and dupilumab for eosinophilic asthma);

however, three additional biologics were assessed in the 2018 class review (mepolizumab, reslizumab, and benralizumab) [1, 2]. While ICER seeks to address the differences in the 2021 review’s analytic modeling approach and provides assumptions within the body of the draft evidence report for “Tezepelumab for Severe Asthma,” it is instead the deterministic point estimates from ICER’s assessments that become the core messages in press releases and summary documents used by the public. Not all stakeholders of ICER’s assessments have health economics and outcomes research backgrounds which would allow them to better understand how changes in the assumptions from the 2018 CE model impacted the CE results for the biologics in the 2021 report.

Implication: The end user(s) may inappropriately compare the incremental CE ratio for asthma biologics in the 2021 assessment with CE results from the 2018 assessment, inaccurately concluding that the treatments in this review are less cost-effective. Adding scenario analyses that replicates the 2018 model assumptions for all asthma populations in this assessment allows for comprehensive comparisons and prevents misinterpretation of current results. Adopting this recommendation will facilitate more informed discussions by the health care decision makers as they evaluate biologic asthma therapies.

2. Remove statements regarding incremental clinical benefits between asthma biologics from the ICER report given the absence of comparative clinical effectiveness evidence.

Rationale: We agree with ICER’s statement about the uncertainties in comparing biologics in the 2021 report: “Populations were not identical across the trials and standards of care have changed, raising the possibility that effects seen in a trial might have been different if used with different background therapy” [2]. Further, the report also acknowledges that there are important uncertainties introduced by the different time periods in which these therapies were assessed this difference in time, affects the background therapies, study design and outcome measurements. In addition, ICER rated the comparative evidence for tezepelumab with Xolair, in patients with allergic asthma as “insufficient” (I), the same evidence rating was given to tezepelumab with dupilumab, in patients with eosinophilic asthma.

In the absence of comparative clinical effectiveness data among biologics, it is inappropriate to draw conclusions regarding the incremental clinical benefit between biologics. However, in multiple places throughout the report, ICER included comparative statements summarizing the clinical effectiveness. For example, “*In the subgroup of patients with allergic asthma, reductions in AAER appear to be somewhat larger with tezepelumab than omalizumab while (small) improvements in daily symptoms and quality of life appear similar to those seen with omalizumab*” and “*In the subgroup of patients with eosinophilic asthma, reductions in AAER and (small) improvements in daily symptoms and quality of life seem similar to those seen*

with dupilumab” [2]. Of note, these summary statements can be highlighted by the public without context and lead to inaccurate interpretations [4, 5].

Implication: ICER risks misrepresenting the comparative clinical evidence in the assessment by making statements that imply an incremental clinical benefit between the asthma biologics, despite insufficient data to compare them. As a result, healthcare decision makers may incorrectly interpret the findings that could negatively impact patient access to valuable asthma therapies.

3. Update the clinical efficacy input for Xolair’s exacerbations resulting in ED visits (without hospitalization) in the allergic asthma scenario analysis.

Specifically, use 0.397 as the rate ratio (RR) for Xolair’s exacerbations resulting in ED visits (without hospitalization).

Rationale: The selection of clinical efficacy inputs substantially impacts the model results and these inputs should be based on the most robust data available. In the scenario analysis for the allergic asthma subgroup as per “*Table E2.7 Key Inputs for Allergic Asthma Scenario Analysis,*” the RR for exacerbations resulting in ED visit (without hospitalization) for Xolair is listed as 0.49 (95% CI: 0.25, 0.97), which is the value for hospital admissions and is incorrect [2]. Per Bousquet et al., 2005, “*Table 5. The rate of hospitalizations and other unscheduled visits for pooled population using Poisson regression,*” the correct RR for ED visits without hospitalization is **0.397 (95% CI: 0.192-0.820)**, p-value 0.013 [6].

Implications: Use of the correct point estimate will yield a more accurate assessment of the effectiveness of Xolair in reducing exacerbations that result in ED visits.

4. Acknowledge Xolair’s published clinical evidence among underserved racial and ethnic minority subgroups when discussing underrepresentation issues in clinical trials.

Rationale: We agree with ICER on the importance of evaluating the impact of asthma therapies for all patients, including racial and ethnic minority subgroups. Although there may be paucity of racial and ethnic minority patients in the trials of tezepelumab, the same is not true for Xolair. When stating “*Black patients were also underrepresented in at least some trials of dupilumab and omalizumab,*” ICER undermines the available evidence on the effectiveness of Xolair treatment across racial and ethnic minority groups and underserved populations who are disproportionately impacted by asthma in the real world.

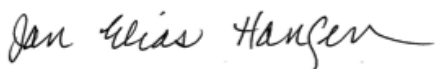
Xolair has specifically been studied in racially and ethnically diverse patient populations in inner-city, low-income pediatric patients, and young-adults (ICATA and PROSE studies) in the United States [7, 8]. Additionally, several Xolair studies included a sufficient number of

patients to perform a *post-hoc* analysis by race (PROSPERO and EXTRA studies) [9]. In aggregate, these data suggest that Xolair is effective in children, adolescents, and adults across diverse racial and ethnic groups with respect to reducing exacerbations, improving symptoms, lung function, and the need for additional medications. The ICER report should reflect the extent to which data are available in these populations as its importance was highlighted in the “Patients and Caregivers Perspectives” section by patients and patient groups [2].

Implication: Discussing the existing evidence for Xolair among racially and ethnically diverse populations will increase the representation, generalizability, and applicability of the findings of this assessment, potentially impacting access to asthma treatments for a real world population.

In conclusion, we are committed to advancing methods to ensure equitable and patient-centric value assessments, and appreciate the opportunity to engage with ICER. We believe incorporating these recommendations will enhance the accuracy of the evidence report, optimize its patient centricity, and provide stakeholders with sufficient information to inform meaningful decisions. We welcome any questions or clarifications on our written communications.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
U.S. Medical Affairs
Genentech, Inc.

References

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**Institute for
Patient Access**



October 12, 2021

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft Evidence Report on Tezepelumab for Severe Asthma

Dear Dr. Pearson:

On behalf of the Institute for Patient Access and Allergy & Asthma Network, we thank you for the opportunity to provide comments regarding ICER's *Draft Evidence Report on Tezepelumab for Severe Asthma*.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

About the Allergy & Asthma Network

Allergy & Asthma Network is the leading national nonprofit organization dedicated to ending needless death and suffering due to asthma, allergies and related conditions through outreach, education, advocacy & research. The Network specializes in sharing patient-friendly, medically accurate information through its award-winning magazine *Allergy & Asthma Today*, E-newsletter, AllergyAsthmaNetwork.org and numerous community outreach programs.

Draft Evidence Report Comments

As ICER finalizes its evidence report, IfPA and AAN urge you to consider several important points.

Clinical Data Shows Tezepelumab to Be an Efficacious Treatment

As the draft evidence report notes, clinical trials indicate that tezepelumab is an efficacious treatment that uses a different mechanism of action. As reported in Allergic Living:

in a large Phase 3 clinical trial, the biologic drug tezepelumab was able to reduce asthma exacerbations by 56% over a year in adult and teen patients with severe, uncontrolled disease. The rate of reduction is considered clinically meaningful.¹

While reporting on the results of its Phase III trial, AstraZeneca noted that tezepelumab is “the only biologic medicine to consistently and significantly reduce AAER [annualized asthma exacerbation rate] in a broad population of severe asthma patients irrespective of baseline eosinophil count.”²

Based on these positive clinical results, tezepelumab is a new and valued treatment option for patients, especially for patients living with severe uncontrolled asthma.

More Treatment Options & New Mechanisms of Action are Valuable to the Asthma Community

Just as asthma impacts people differently, existing treatment options serve some patients better than others. Some people’s asthma conditions are mild or moderate, and intermittent symptoms may be well controlled by the current standard of care. Others live with severe asthma, which may or may not respond to the current standard of care. For those who don’t respond to existing treatments, their asthma may progress to a more severe or uncontrolled state. And, while asthma symptoms have an impact on patients’ lives regardless of severity or frequency, severe asthma in particular can reduce quality of life and hamper patients’ ability to sleep, maintain mental health, exercise, stay focused at work or school, or participate in social or extracurricular activities.

These considerations are complicated by the reality that asthma is a chronic disease that will often impact people over their entire lives. The severity of the disease tends to worsen as people age, which can be complicated by waning efficacy of patients’ current treatments over time. The fact that current treatments are controlling patients’ asthma symptoms today does not guarantee that their symptoms will be well controlled tomorrow.

Existing medications, including targeted biologic therapies, prove valuable and effective for many asthma patients. Through increasing efficacious treatment options by introducing a new mechanism of action, tezepelumab increases the likelihood that patients and their clinicians can find an effective regimen to control the disease and its symptoms – reducing dangerous or expensive exacerbations, added physician appointments and visits to the ER.

As a new medicine with a novel mechanism of action, tezepelumab represents an important addition to the asthma community’s treatment options. While the value of expanding treatment

¹ Goodwin J and Smith G “Dupilumab Remission; Tezepelumab in Severe Asthma” Allergic Living, March 2, 2021, <https://www.allergicliving.com/2021/03/02/aaaai-news-dupilumab-remission-tezepelumab-in-severe-asthma-palforzia-safety/>.

² <https://www.astrazeneca.com/media-centre/press-releases/2021/tezepelumab-is-the-first-biologic-to-consistently-and-significantly-reduce-exacerbations-in-broad-population-of-severe-asthma-patients.html>.

options is difficult to quantify, it is imperative that these considerations be documented in the final evidence report.

Severe Uncontrolled Asthma Exacts a High Cost

These considerations are particularly important for people living with severe asthma and for whom the current standard of care is ineffective, including people with severe uncontrolled asthma. As noted in the draft evidence report, the CDC estimates that 25 million Americans are living with asthma, and that patients with severe uncontrolled asthma represent an estimated 5-10% of total asthma cases.³ These figures suggest that there are currently between 1.3 million and 2.5 million people in the United States living with severe uncontrolled asthma.

Severe uncontrolled asthma meaningfully reduces patients' quality of life and, in extreme cases, can even be fatal. In fact, severe uncontrolled asthma is recognized as a "major unmet medical need" by the medical community.⁴ Based on the current clinical trial results, tezepelumab will help fill this major unmet medical need. If properly applied to the small share of patients with severe uncontrolled asthma, the total societal cost estimates cited in the draft evidence report provide a useful benchmark for understanding the potential value of tezepelumab.

As the draft evidence report documents, the total societal costs are an estimated \$82 billion, inclusive of direct medical costs, asthma-related mortality, and missed work and school. As with most diseases, however, these societal costs are not evenly distributed across all patients. Instead, a small minority of patients bear a disproportionate share of these costs. In the case of asthma, it is the patients living with severe uncontrolled asthma who bear a disproportionate share of the costs.

According to a study in the *Journal of Allergy and Clinical Immunology*, "retrospective claims research indicates that approximately half of asthma-related direct costs are incurred by patients with severe asthma."⁵

Worth noting, the health and economic burdens of severe and uncontrolled asthma are projected to significantly grow in the future, increasing still further the value of an efficacious treatment. Looking at the costs of uncontrolled asthma over the long-term, Yaghoubi et. al. estimated the 20-year direct costs to be \$300.6 billion, or a total economic burden of \$963.5 billion when indirect costs are included. The researchers expect American adolescents and adults to "lose an estimated 15.46 million QALYs over this period because of uncontrolled asthma."⁶

³ See also, Kupczyk M and Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *J Intern Med* 2012; 272:121–32. Wenzel S. Severe Asthma in Adults. *Am J Respir Crit Care Med*. 2005; 172; 149–60.

⁴ Kupczyk M and Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *J Intern Med* 2012; 272:121–32.

⁵ Hankin CS, Bronstone A, Wang Z, Small MB, and Buck P "Estimated Prevalence and Economic Burden of Severe, Uncontrolled Asthma in the United States" *The Journal of Allergy and Clinical Immunology*, Volume 131, Issue 2, February 1, 2013, [https://www.jacionline.org/article/S0091-6749\(12\)03119-3/fulltext](https://www.jacionline.org/article/S0091-6749(12)03119-3/fulltext).

⁶ Yaghoubi M, Adibi A, Safari A, FitzGerald JM, and Sadatsafavi M "The Projected Economic and Health Burden of Uncontrolled Asthma in the United States" *American Journal of Respiratory and Critical Care Medicine*, June 5, 2019.

Per-Patient Costs Better Reflect the Expense of Severe Asthma & the Value of Effective Treatment

Assuming the costs associated with asthma-related mortality and missed work and school are due to severe asthma, patients living with uncontrolled severe asthma account for \$57 billion of the total costs of asthma, or per-patient costs up to nearly \$44,000. These substantial per-patient costs signify the high value of an efficacious medicine that can control or lessen severe asthma symptoms and help lower the current costs borne by severe asthma patients and their families.

The cost-effectiveness analysis should explicitly account for the \$44,000 in per-patient costs due to severe uncontrolled asthma when evaluating the value of tezepelumab. It is, consequently, imperative that the final evidence report incorporate these higher but more applicable per-patient costs estimates and acknowledge the reality that the costs associated with severe uncontrolled asthma will likely increase significantly without access to an effective treatment.

The Cost-Effectiveness Analysis Should Account for Severe Asthma's Demographic Disparities

The draft evidence report should also more fully account for the reality that African American, Hispanic and Native American communities bear a larger burden from asthma than do other demographic groups. Some of the troubling trends include:⁷

- Black Americans are nearly 1.5 times more likely to have asthma, five times more likely to visit the emergency room due to asthma, and three times more likely to die from asthma compared to white Americans
- Puerto Ricans are twice as likely to have asthma and have a nearly three-fold higher rate of asthma-related deaths than the broader Hispanic and white populations in the United States
- Native Americans are nearly twice as likely to experience asthma symptoms every day and have a 10% higher risk of death from chronic lower respiratory diseases relative to white Americans.

In evaluating the value of tezepelumab for people with severe and uncontrolled asthma, the disproportionate impact of asthma on people of color is an important consideration. We urge ICER to account for these impacts in its final report.

Cost Assumptions Do Not Account for the Temporary Nature of Product Exclusivity

The lifetime cost estimates do not appear to account for the temporary nature of product exclusivity. Even if the draft evidence report's assumed price were accurate in the short term, the price for the medicine should be expected to decline over time once product exclusivity expires. For instance, as GoodRx has noted, while the average cash price for branded Advair was \$496 in 2018, "the lowest GoodRx price for the most common version of generic Xopenex HFA is around \$32.39."⁸

⁷ <https://www.aafa.org/asthma-disparities-burden-on-minorities.aspx>.

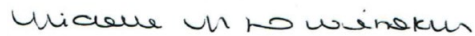
⁸ Marsh T "Here's Why Asthma Inhalers Are So expensive" GoodRx, June 8, 2020, <https://www.goodrx.com/conditions/asthma/heres-why-asthma-inhalers-are-so-expensive>.

As with other chronic diseases, the costs of asthma medication will stretch across a lifetime. Since the average market exclusivity period is around 12 years, it is reasonable to expect the price of the tezepelumab to decline over time, which will significantly reduce the expected lifetime treatment costs. Lower lifetime treatment costs will meaningfully alter the cost-effectiveness of tezepelumab, even at the assumed price. The final evidence report could offer a more realistic outlook were it to account for competition's impact on medication costs over the relevant study timeframe.

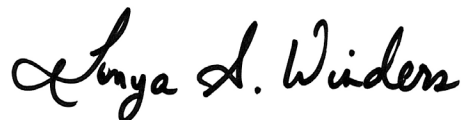
Conclusion

IfPA and AAN urge ICER to address our concerns related to this draft evidence report. Based on the current iteration, ICER's analysis provides an inaccurate picture of the benefits created by tezepelumab for the treatment of asthma. If IfPA or AAN can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its report, please contact IfPA at 202-951-7097.

Sincerely,



Michelle M. D. Winokur, DrPH
Executive Director
Institute for Patient Access



Tonya S. Winders
President and CEO
Allergy & Asthma Network

October 12, 2021

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft evidence report for severe asthma therapy tezepelumab

Dr. Pearson:

I appreciate the opportunity to provide comments regarding ICER's *Draft Evidence Report on Tezepelumab for Severe Asthma*.

As a physician practicing in Montgomery, Alabama, I have over 30 years of experience treating patients with a wide range of allergic illnesses and asthma. I am the current Past President of the ACAAI, and also serve on the Advocacy Council of ACAAI, Budget and Finance Committee, Board of Regents and Executive Committee.

As ICER moves towards the final Evidence Report and Presentation, I urge you to consider several important points.

The Cost of Severe Asthma

As acknowledged in the drafted report, the CDC estimates that 25 million Americans are living with asthma and that 5-10% of these patients have severe, uncontrolled asthma. For this population of patients, the current standard of care often does little to manage symptoms and prevent exacerbations. This small cohort of patients consumes much of the estimated \$82 billion of societal costs, costs that are only expected to grow in coming years.

While the economic burden to society is notable, the impact on individual patients should not be lost. In my experience working with patients, I find that patients with severe asthma face a significant loss in quality of life, experience difficulty sleeping, and often miss work/school.

It is also critically important to recognize that asthma disproportionately impacts certain demographics. Minority communities, specifically African Americans, Hispanic Americans and Native Americans, not only face higher rates of asthma, but higher rates of negative health outcomes due to asthma. It's important to recognize the disproportionate impact on people of color.¹ The Affordable Care Act makes it illegal to discriminate against these groups through healthcare system design. In my opinion, your processes are inherently discriminatory against these groups.

¹ <https://www.aafa.org/asthma-disparities-burden-on-minorities.aspx>.

Variety of Treatment Options

In recent years a number of asthma treatments have been developed and come to market, which provide great hope for me as a doctor and also for my patients. For many patients, these innovative medicines have a striking impact on quality of life. However, asthma is a wide-ranging disease that impacts patients in a variety of ways. Despite these new medications, there are still a large number of patients who struggle to control their symptoms.

Tezepelumab is unique to these treatments, as it has a different mechanism of action. As a TSLP inhibitor, tezepelumab works higher in the inflammation pathway. Due in large part to positive results in Phase II trials, tezepelumab was granted “breakthrough” status by the FDA.² However, the FDA has not completed their review. I urge you to reconsider issuing a recommendation without the full complement of data. The addition of this treatment to those currently available could prove valuable to many patients. Despite the recent improvement in asthma treatments, there is still a significant unmet need amongst severe, uncontrolled asthma patients. Tezepelumab could go a long way to help satisfy that need.

Flaws of the Quality Adjusted Life Year

ICER’s continued reliance on the quality adjusted life year is of great concern. The idea behind the QALY, placing a price tag on the value of living a year of health, is inherently flawed. The usage of QALYs is also discriminatory in nature. For a patient who is disabled, they will be unable to achieve a maximum score on the QALY scale, as they cannot achieve the highest “quality of life”.³ Similar issues arise for patients of chronic conditions, such as asthma. Treatments targeted at patients whose potential for health is diminished due to chronic conditions may be given a lower QALY score. Because of these concerns, Congress has banned the QALY in cost-effectiveness reviews by the Medicare program.

While ICER notes that the QALY is a commonly used metric in cost-effectiveness analyses, it’s important to recognize that the QALY does not evaluate clinical analysis. Garrison et al. went as far as to say that the QALY does not always capture the health or well being of patients. It also fails to incorporate factors such as disease severity, equity of access, or unmet need and I urge you to recognize its limitations.⁴

Many argue that there are no better measures of quality adjusted life years. By analogy, this is like saying since we don't have any boats without massive holes in the hull, we should sail in this one with the smallest holes, since we will not sink as soon. I'd say build a better boat and stay on shore until then. To many of us, your use of QALY renders your report of no value.

² <https://pubmed.ncbi.nlm.nih.gov/32078149/>

³ <https://cevr.tuftsmedicalcenter.org/news/2019/pipcreply>

⁴ Garrison et al., Value in Health (21) 2018, 161-165

Conclusion

As a physician who understands the necessity for treatments in the severe asthma space, I urge you to consider my comments regarding this draft evidence report. It is imperative that this review provides an accurate picture on the potential benefits of adding tezepelumab to the available treatment options for severe asthma. If I can be of any assistance to ICER as they finalize the evidence report, please contact me at jallenmeadows@gmail.com.

Sincerely,

J. Allen Meadows, MD

Dr S D Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
BOSTON MA 02109

10 October 2021

My dear Dr. Pearson

PUBLIC COMMENT FOR REVIEW OF TEZEPelumAB FOR SEVERE (UNCONTROLLED) CHRONIC ASTHMA

I refer to your recently released Draft Evidence Report for Tezepelumab for Severe Asthma ¹.

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science ^{2 3}. That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales, and simple logic in driving claims by assertions and assumptions. The tezelpelumab report is no exception.

While you might view your standards and reports, and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. The QALY, for example, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in *F1000Research* and a letter to *Value in Health* pointing this out ^{4 5}.

I would like to focus on the preference scores that you invent as part of the modelling exercise. Central to the ICER assumption driven simulated imaginary claims is the QALY. This forms the basis for imaginary incremental cost-per-QALY claims and the application of QALY thresholds. Time spent is multiplied by a preference score to create a QALY. As detailed in previous correspondence this is mathematically impossible as the preference score has negative values which means it lacks a true zero and cannot support multiplication; this requires a ratio measure ⁶. In the asthma model, there is no direct elicitation of ordinal preference scores (in this case the EQ-5D-5L) from patients; rather a linear transformation (utility mapping) of the ordinary least squares form:

$$EQ-5D-5L = 0.14 + 0.12 AQLQ$$

where AQLQ is the Asthma Quality of Life Questionnaire score (no other information on the model fit is provided which is unfortunate). The report states:

*Without commonly used utilities reported in the tezepelumab trials, we relied on evidence of patient reported outcome instruments with known utility mappings. The non-exacerbation health state utility value is specific to the evidence for tezepelumab plus SoC versus SoC alone. Evidence from tezepelumab trials (NAVIGATOR, PATHWAY, and Amgen data on file) include the responses from the Asthma Quality of Life Questionnaire (AQLQ) to derive utility values using the conversion from the AQLQ to the EQ-5D-5L. The least squares mean change and 95% confidence intervals from the AQLQ for tezepelumab plus SoC versus SoC alone provide the inputs for the aggregate mapping algorithm ($EQ-5D = 0.14 + 0.12 * AQLQ$ score). Disutilities for the exacerbation health states and for chronic OCS use were assumed to be the same across treatment strategies (pg. 19).*

Unfortunately, there are a number of issues associated with this mapping function which are not addressed by the authors and which render it invalid or, more properly, rubbish.

Consider the AQLQ instrument ⁷. This is a 32 item-questionnaire used to assess the physical, occupational, emotional and social qualities of adults 17 to 70 years exhibiting mild to moderate asthma. It is a multiattribute instrument with four domains: symptoms (12 items), activity limitation (6 generic and 5 patient-specific items), emotional function (5 items), and environmental stimuli (4 items). Each item response is on a 7 point Likert scale with responses ranging from 1 = maximal impairment to 7 = minimal impairment. The items are in the form of questions with each of the scale points anchored on a word or phrase and not just the extreme values; descriptors include “totally”, “extremely”, “very”, “moderate”, “some” “a little”. As Wilson et al note: some of these scales may be confusing to respondents as they mix adjectives with other grammatical elements and that there is no published evidence that the anchor words and phrases can be consistently ordered independently of their numerical positioning on the response scale or that the relative positions of different phrases represent approximately equal psychometric intervals ⁸. A common feature of Likert scales. The fact that it has shown strong classical measurement properties is irrelevant; this only occurs if you ignore the axioms of fundamental measurement and assume the AQLQ has interval properties for the Likert scores (which could equally well be designed on a 7 point scale as A,B,C,D,E,F,G rather than with a numeric assignment or even an emoji). Just as we can't interpret the 'numerical' distance between A and B, we can't interpret the distance between 1 and 2. Indeed, is 2 actually greater than 1 and less than 3 (or is B actually greater than A and less than C)? Will different subjects treat the same responses differently?

As Likert scales are ordinal scales this means the AQLQ combines 32 Likert scales none of which, if we follow the axioms of fundamental measurement, can support averages as the distances between the scores are unknown. At best ordinal scales can only support, if we accept that they can be ordered, medians and modes and non-parametric statistics. An ordinal score, unless you assume otherwise, cannot support the arithmetic operations of addition, subtraction,

multiplication or division. Interval scores, with invariance of comparison, can support addition and subtraction; ratio scales as they have a true zero can also support multiplication and division. Nevertheless, the scoring of the AQLQ ignores these requirements of fundamental measurement and treats the scales, either through ignorance or design, as if they had interval properties. This allows an average score to be created for each ordinal Likert scale with domain and aggregate scores created by merging the average Likert values for each for each item. It is surprising that, after some 30 years, the limitations of fundamental measurement have not been addressed in respect of the AQLQ.

As well as average values (in range 1 to 7) the AQLQ has the following characteristics: it is dimensionally heterogeneous (not unidimensional) and lacks construct validity. The aggregate AQLQ score is meaningless; we have no idea of the distance between the overall scores or what interpretation, if any, we should place on them. Furthermore, as the AQLQ is an ordinal score it should not be utilized in regression modelling where the requirement is for continuous independent variables to have ratio, or at best, interval measurement properties (i.e. invariance of comparison). To describe the average AQLQ score as a 'score' is a misnomer; it is a value that results from illegitimate manipulations of Likert scales to produce a 'number' that is meaningless.

Putting aside these minor concerns, consider the ersatz EQ-5D-5L preferences that are created by this transformation by least squares algorithm. These are defined as preferences (presumably still ordinal) that lie in a range from 0.28 to 0.98. These values are, presumably, intended to be a subset of the 'master', EQ-5D-5L scales with a range, using the US valuation from -0.573 to 1.0⁹. This means that the asthma utilities, as a subset, do not have a true zero; they cannot be viewed as being in a range from 0 = death to 1 = perfect health (with floor and ceiling constraints) but rather as part of the EQ-5D-5L scales where 20% of health states are worse than death. The fact that these 'created' values, implicit health states, are valued as greater than zero is just happenstance. Direct valuation with the EQ-5D-5L of mild to moderate asthma patients could well produce negative values, although (in common with the AQLQ) this multiattribute instrument is dimensionally heterogeneous (multidimensional) and lacks construct validity as a bundle of attributes^{10 11}. The created values are part of a preference score which, while not created directly from mild to moderate asthma patients, are still bound by the author's claim that they are 'true' EQ-5D-5L preference values. Unfortunately, this raises a further barrier: EQ-5D-5L scores are ordinal and lack a 'true zero'. They cannot be used in a multiplicative mode to create QALYs as the authors of the asthma model proceed to do. Unless, of course, ICER and the expert simulation model group makes a further assumption, as ICER believes, that these EQ-5D-5L ordinal preferences are a ratio measure in disguise.

What is overlooked in the creation of instruments such as the AQLQ and EQ-5D-5L is that if you are aware of the axioms of fundamental measurement then the instrument has to be designed to have those measurement qualities; it cannot be assumed to have the required properties *ex post facto*. Set against the standards of interval and ratio scales both the AQLQ and the EQ-5D-5L fail. Yet they continue to be applied.

Quality of life is not an elusive concept. If the authors of this mapping absurdity want an example of a quality of life measures that meets the required standards of fundamental

measurement for a single coherent latent construct then they might consider the Asthma Life Impact Scale (ALIS) that was developed some fifteen years ago¹². The rationale for ALIS was that the focus of patient reported outcomes measures in asthma, such as the AQLQ, on symptoms and functioning (which can be captured as separate attributes) rather than a holistic, single latent construct approach, with the question: to what extent is the need of asthma patient's being met. In other words, what is the overall impact of a therapy on the patient's quality of life; the conceptual framework is that quality of life is dependent on an individual's ability to fulfill fundamental needs and that their quality of life is high when these needs are met. With the application of Rasch Measurement Theory, the Rasch model, items are selected to reflect a single underlying unidimensional construct with face and content validity, together with overall construct validity. Scores on the final version of ALIS ranged from 0 to 22 with a high score indicating a major negative impact of asthma where each item elicits a binary response of True/Not true. It is now accepted that multiattribute instruments such as the EQ-5D-5L are long past their use-by date, ALIS is intended to be used alongside other single attribute measures of symptom and functioning to allow patients to describe the full impact of their condition and response to therapy options in a trial environment.

It is clear that the authors of the algorithm are at a loss when it comes to measurement theory. Our focus must be on interval level measures (the AQLQ and EQ-5D-5L are not) which as Steven's pointed out in the 1940s, can only occur if we allocate numbers to events according to certain rules. Rules which are central to RMT and where the Rasch model provides the basis for fundamental measures. This points to a critical distinction between classical test theory (CTT) which has been used to justify and endorse the AQLQ, and RMT to support ALIS. The former is exploratory and descriptive and must account for all the data while the latter is confirmatory and predictive requiring the data to fit the model. The Rasch model focuses on the size and structure of residuals where the principle of conjoint simultaneous measurement is sufficiently realized to justify the claim that the results can be used as a measurement scale with invariant, interval measurement properties¹³.

More recently a transformation algorithm has been developed to translate disease specific interval measures such as ALIS into bounded ratio scores¹⁴. This gives, for the first time, a coherent unidimensional measure of quality of life that evaluates the extent to which need is met and the response to therapy options in disease specific quality of life terms. We are now in a position to abandon instruments such as the AQLQ and the absurd EQ-5D-5L (including the nonsense of a mapping algorithm to create one ordinal scale from another) in favor of those which meet required fundamental measurement standards.

ICER has two options: (i) to withdraw the assumption driven simulation model for asthma pricing; or (ii) to claim that, by assumption, the AQLQ actually creates interval scores and that the mapping algorithm creates "true" ratio EQ-5D-5L preferences. Under (i) ICER would recognize the limitations imposed by fundamental measurement and that the QALY is mathematically impossible while, under (ii), ICER would admit its models rest on assumptions and nothing more and are not intended to meet the standards of normal science. My inclination would be that ICER will take option (ii) under the defense that 'everyone else does it'; which is not only weak but demonstrably false. There are many

activities which people partake in, yet not ones we would wish to emulate. After all, we can hardly quibble over an imaginary assumption driven simulation model if the authors introduce further assumptions to deny the axioms of fundamental measurement. What is one further assumption among the many that drive the ICER imaginary simulation?

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October 15, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report on severe asthma. Asthma impacts about 25 million Americans, and it is a condition that disproportionately impacts Black and Hispanic patients. With this in mind, it is important that ICER handle this assessment in a way that does not exacerbate health inequities that are already very prevalent in the asthma community. PIPC requests ICER consider the following comments.

ICER's model is unrepresentative of real-world settings.

ICER takes its baseline inputs from placebo rates from randomized clinical trials (RCT) not from real world data – this makes the model unrepresentative of real-world settings.

The annual probability of an exacerbation of 1.82 per year was taken from the RCT placebo arms. We know that RCT populations are typically far healthier than the actual indicated population for the treatment. In the case of asthma, this is particularly concerning as communities of color are typically underrepresented in RCTs, and there are major racial disparities in the burden of asthma in the United States. A recent report by the Asthma and Allergy Foundation of America found that non-Hispanic Black Americans are almost three times as likely to die from asthma-related causes than non-Hispanic white Americans.¹

Recent studies designed to estimate the real world rate of exacerbation in a severe asthma population have showed a much higher rate of exacerbation, ranging from 2.68-3.97 per year;²

¹ Asthma and Allergy Foundation of America, "Asthma Disparities in America" (2020). <https://www.aafa.org/asthma-disparities-burden-on-minorities.aspx#pdf>. Accessed October 4, 2021.

² Llanos JP, Ortega H, Bogart M, Packnett ER, Manjelienskaia J, Bell CF, Hahn B. Real-world effectiveness of mepolizumab in patients with severe asthma: an examination of exacerbations and costs. *Journal of asthma and allergy*. 2020;13:77.

2.195 - 2.687 per year;³ 2.7 per year;⁴ 4.92 per year;⁵ and as much as 8.3 per year.⁶ All of these studies suggest a baseline exacerbation rate of at least 50% higher than that used by ICER and some suggest a rate greater than 400% higher than that used in the ICER model.

This reliance on RCT data, which does not include a representative population of asthma patients, leads to a model that underestimates the burden of the disease and as such an underestimate of the value of any incremental treatment effect.

PIPC continues to express concern with ICER’s consistent use of the Quality-Adjusted Life Year (QALY).

PIPC has consistently voiced concern with ICER continuing to rely on the QALY in its assessments despite its discriminatory implications for people with disabilities. In addition to its discriminatory impacts for people with disabilities, traditional cost-effectiveness assessments relying on the QALY have similarly discriminatory implications for communities of color, which bear a heavier burden of disease in asthma.

Most cost-effectiveness assessments rely on data from RCTs (issues with which we have touched on above) and health utility preference weighting surveys, which rely on inputs from primarily Caucasian populations. These assessments are largely based on outcomes to the “average” patient and do not account for patient subgroups. This means key components like social determinants of health are not captured, and ultimately treatments that may be very effective for minority populations can be undervalued.⁷

The model makes the likely incorrect assumption that the reduction in risk of exacerbation at 52 weeks seen in the RCTs is the peak of the treatment’s effectiveness.

Several studies have shown that the impact of continued biologics use improves over time.⁸ Effectiveness (particularly reduced exacerbation rates) improves year after year for at least four

³ Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC pulmonary medicine*. 2017 Dec;17(1):1-1.

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⁶ Ibrahim H, O’Sullivan R, Casey D, Murphy J, MacSharry J, Plant BJ, Murphy DM. The effectiveness of reslizumab in severe asthma treatment: a real-world experience. *Respiratory research*. 2019 Dec;20(1):1-5.

⁷ National Minority Quality Forum et al. “Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities.”

⁸ Schleich F, Graff S, Nekoe H, Moermans C, Henket M, Sanchez C, Paulus V, Guissard F, Donneau AF, Louis R. Real-world experience with mepolizumab: Does it deliver what it has promised?. *Clinical & Experimental Allergy*. 2020 Jun;50(6):687-95.

years. This is not a factor that has been incorporated into the model, which only assumes the rate achieved in the RCT at year one.⁹

The choice of disutility for exacerbations used in the ICER model is an underestimate.

ICER calculated the disutility of an exacerbation from a study undertaken in the UK, which estimated that the health state utility of an asthma patient without exacerbation was 0.89, an exacerbation that did not lead to hospitalization would have a utility of 0.57, and an exacerbation that led to hospitalization a utility of 0.33.¹⁰ This would mean the disutility of a non-hospitalized exacerbation is -0.32 (0.89-0.57) and the disutility of an exacerbation that leads to hospitalization is -0.56 (0.89-0.33).

Yet, the ICER model uses a disutility of 0.1 and 0.2 for these two states, despite referencing this study as its source. It seems the cause of this error is misinterpretation of the data. A fourth column in table 2 of Lloyd (2007) represents the mean change in utility over the course of the data collection period and the estimates for this fall over time within states was 0.1 and 0.2 respectively. We believe these data were mistakenly used as estimates of mean disutility for exacerbation without hospitalization and exacerbation with hospitalization in the model.

In addition, the study also states that these utilities represent the mean for the patients over a one-month period for which data was collected. The ICER model applies these utilities for just 2 weeks (a single model cycle), so even if the disutilities used were correct, they would be providing half of the absolute disutility associated with the exacerbations themselves.

Taking into account both of these elements, the ICER model underestimates the disutility of exacerbation, and the absolute disutility for an exacerbation in the model is approximately one sixth of what it should be. As net benefit in the model is based largely on the rate and severity of exacerbations this means the incremental gain in health utility is likely to be six times higher than those calculated by the ICER model.

Conclusion

First, PIPC urges ICER to review the technical components of the model to ensure it is providing accurate results. Second, PIPC cautions ICER about the use of a QALY-based cost-effectiveness analysis relying on RCT data to evaluate treatments for asthma. It is likely that this will underestimate their benefit for patients and people of color and continue to exacerbate health disparities already experienced by asthma patients.

⁹ Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, Brightling CE, Griffiths JM, Hellqvist Å, Bowen K, Kaur P. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *New England Journal of Medicine*. 2021 May 13;384(19):1800-9.

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Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

October 12, 2021

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
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Re: Draft evidence report for severe asthma therapy tezepelumab

Dr. Pearson:

The price of asthma for children and their families

As a respiratory therapist (RT) and asthma educator (AEC certified) at a major children's hospital in the South, the cost of severe asthma is more than a few days in our Pediatric ICU. Our facility has several services for children with severe asthma and their families. These services range from an outpatient asthma clinic to an intense and stressful hospitalization. Let's take a look at a family with a child with severe asthma who is having an asthma attack.

For many asthmatics an attack often begins as a result of the common cold. So many of us take for granted something as simple as the common cold because it's just a cold right? The child presents to a hospital, urgent care center or doctors' office with status asthmaticus. They treat the child as best they can and then we get a call to our call center to dispatch an ambulance to transport the child to our specialty hospital. A nurse and RT (full transport ambulance or flight team) are dispatched. We service outside facilities if the child has to be intubated or if the child is just not getting any better. Upon arrival to the outstanding hospital, the RT and RN work vigorously to help him breathe. Fighting for time and to get the child stable, the RN and RT administer continuous breathing treatments, Heli-ox, steroids, if not already started, and magnesium. They Intubate if necessary. This could also mean physically pushing on a patients' chest to get air out of his lungs. Many kids also come straight to our emergency room via outside ambulance.

Upon arrival to the children's hospital emergency department or direct admit to Pediatric ICU we continue to monitor and assess the patient for progress or deterioration. If they're still in respiratory failure despite conventional ventilation, we'll attempt High Frequency Oscillation Ventilation (HFOV). What a pneumothorax? We'll attempt Isoflurane. Our facility uses a one-on-one RT for isoflurane administration for the first 24 hours. It requires close monitoring of the patient's blood gasses and temperature. Inhaled isoflurane is an anesthesia gas that acts like a bronchodilator in the most severe cases of asthma. Last but not least, ECMO- Extra-Corporal Membrane Oxygenation. This requires several units of blood, a surgeon, and bedside on call OR team. We have to preserve more than lung tissue, at this point the kids' fragile brain sets them up for anoxic brain injury. This timeline can occur sometimes in a matter of hours of reaching our doorstep to several weeks in the ICU.

Not only do we treat the child, the parents may also require attention from lack of sleep and not eating. Many families use continuous or intermittent FMLA to spend time and help with their child's recovery. The child loses time from school due to hospital stay and follow-up appointments. The specialty doctors for this child includes a pediatric pulmonologist, asthma-allergy specialist, and in some cases ENT (Ear, Nose, Throat).

Finally, when discharge is on the horizon, that's when we start working on prevention of future asthma status asthmaticus. Every patient that is admitted to our hospital presenting with asthma has to attend an asthma class. If they get admitted 5 times, they come to asthma class 5 times. We discuss the medicines and alternatives plus an Asthma Action Plan. Sadly, I will have a mom in my class crying that their baby was started on a biologic and insurance, for whatever reason, stopped covering the injections. They would do great on Omalizumab and then their entire world comes crashing down when they stop covering the injections and their child is back in the PICU with the same scenario.

I often ask parents to take care of their own mental health as well as take care of their child. I highly recommend meditation to families and patients. As a healthcare worker it is difficult to come home and release from such frustrating circumstances. Not all kids end up in the hospital due to noncompliance of drugs. For some, it can be a factor of not having money for daily meds after insurance pays their part. It's no secret that the more medicines we have for asthma, the more choices parents have, the better chance of adherence to an asthma regimen. The cost goes down! While injection biologics are not cheap, it pales in comparison to the cost of the story mentioned above. The amount of time, money, and resources for severe asthma has to start with prevention.

Thank you for the opportunity to comment on this review.

Sincerely,

Phylliscia Gibson MPH RRT NPS AEC

Tracheostomy/ Asthma Educator

October 14, 2021

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via email: publiccomments@icer.org

RE: Draft Evidence Report for the Assessment of “Tezepelumab in Severe Asthma”

Dear ICER Review Team:

Sanofi and Regeneron Pharmaceuticals appreciate the opportunity to provide comments on ICER’s draft evidence report titled “*Tezepelumab for Severe Asthma*” in which dupilumab (DUPIXENT®) is included as a comparator.

Dupilumab is approved in the US as “*add-on maintenance treatment in patients with moderate to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma*”.¹ For these patients, the recommended dose of dupilumab for adults and adolescents (12 years of age and older) is: “*an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week, and for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week. Dupilumab is not for the relief of acute bronchospasm or status asthmaticus*”.

KEY OBSERVATIONS

Sanofi/Regeneron believes that the report can benefit from greater clarity in the description of type 2 inflammation in asthma as well as the role of dupilumab as a biologic that suppresses type 2 inflammatory pathways. As the report acknowledges, type 2 inflammation refers to innate and adaptive immune responses including T helper 2 (Th2) driven activation of key cytokines IL-4, IL-5 and IL-13. These cytokines lead to downstream activation of local and systemic inflammatory cells including eosinophils, mast cells, macrophages and goblet cells. In asthma, this can lead to eosinophil trafficking into tissue, increased IgE production as well as goblet cell hyperplasia and mucus production² among many processes. Type 2 inflammatory asthma is present in most patients with severe asthma³, and includes patients that are characterized as having “allergic asthma” or “eosinophilic asthma”. There are several biomarkers that can be used to identify patients with type 2 inflammatory asthma, including blood or sputum eosinophils, exhaled nitric oxide (FeNO), and peripheral IgE levels.⁴ Efficacy across multiple biologics has been evaluated in populations identified on the basis of these biomarkers, including blood eosinophils, FeNO and peripheral IgE.⁴ The subtype “allergic asthma,” has been identified by peripheral IgE levels, atopy, or other associated clinical features, and the subtype “eosinophilic asthma” has been identified on the basis of peripheral or sputum eosinophils. However, it is important that the report recognize that there are not consensus thresholds for these biomarkers to define these subtypes, and efficacy has been demonstrated using different threshold for different biomarkers. As there is not consensus definition of this term, the preference would be to use precise terminology when providing results of trials, for example “patient with blood eosinophils \geq 150 cells/uI”.

Dupilumab has a unique mechanism of action compared to available biologics for the treatment of asthma, and blocks the shared receptor component for IL-4 and IL-13, which are key drivers of type 2

inflammation in multiple diseases.⁵ Dupilumab has demonstrated clinical efficacy across multiple type 2 inflammatory asthma subtypes, including patients identified by baseline blood eosinophils \geq 150 cells/ul, patients with baseline FeNO \geq 25 ppb⁶ (\geq 20 ppb in children⁷) and patients with uncontrolled moderate-to-severe asthma and evidence of allergic asthma.⁸ While the report recognizes the efficacy of omalizumab for patients with an allergic phenotype, the dupilumab efficacy in this patient population should also be recognized.

Sanofi/Regeneron agree with ICER’s acknowledgement of dupilumab’s clinical benefits in OCS-dependent asthma. OCS-dependence is a clinical feature of type 2 inflammation.⁹ Unlike tezepelumab, dupilumab has demonstrated efficacy in patients with OCS-dependent asthma, significantly reducing OCS use while also decreasing the rate of severe exacerbations and improving lung function and asthma control.¹⁰

Sanofi/Regeneron believe that the long-term safety and efficacy of medicines is a crucial element when assessing their value. In ICER’s 2018 review of the use of biologics in asthma, it acknowledged that *“there is a lack of evidence on the long-term safety and effectiveness of these drugs”*. However, we provided ICER with multiple references^{11,12,13,14,15,16} on dupilumab’s long-term data, including safety and efficacy in a population that has been exposed to dupilumab for up to three years in clinical trials.¹⁷

Sanofi/Regeneron agree with ICER’s recognition that there are fundamental differences between dupilumab in trial populations, endpoints and indications making cross-trial comparisons difficult. The trials were designed to evaluate different populations using two compounds with very different mechanisms of action. QUEST was the pivotal phase 3 study that evaluated dupilumab efficacy in patients with moderate-to-severe asthma. NAVIGATOR was the pivotal phase 3 trial that evaluated tezepelumab efficacy in patients with severe asthma. Asthma severity denotes the level of treatment required to control symptoms and exacerbations, and reflects a complex interplay between exacerbation frequency, lung function, asthma control and quality of life. Each of these features impacts the other and selecting a population with more “severe” disease naturally selects patients with different relationships between these features of disease.¹⁸ Specifically, the trial populations for QUEST and NAVIGATOR had different inclusion requirements for the frequency of baseline exacerbations, background corticosteroid use, and baseline blood biomarkers. Patients with frequent asthma exacerbations are a population with more severe disease, greater risk of loss of lung function,¹⁹ and exacerbation frequency is an important and independent predictor of future exacerbations.^{20,21} Asthma exacerbations are associated with increased levels of peripheral and sputum eosinophils,²² and may denote patients that are more likely to have asthma driven in part by type 2 inflammation, supporting the rationale for differential response to targeted therapies.

DETAILED COMMENTS AND RECOMMENDATIONS

Suggestions for change are highlighted in red.

Page	Original text	Suggestions for Text Changes or Comments
ES2	This is also true of dupilumab, and long-term studies of dupilumab provide additional evidence of safety. (Missing references)	<p>Comment: Please include appropriate references to support dupilumab long term data.</p> <p>Recommendation: Please update statement as follows: This is also true of dupilumab, and long-term studies of dupilumab provide additional evidence of safety.^{23,24,25,26,27,28,29}</p>
8	Although an exact definition of eosinophilic asthma does not appear in	<p>Comment: We would suggest separating the concept of “eosinophilic asthma” from patients identified based on baseline</p>

	the label, a cutoff of ≥ 150 cells/ μL is typically used.	<p>eosinophil thresholds in order to provide greater clarity regarding which populations are being referenced. The term “eosinophilic asthma” appears in the dupilumab, mepolizumab and benralizumab indication statements, however there is not a consensus definition for which eosinophil threshold this refers to, and this phenotype may refer to patients identified by different eosinophil thresholds across different biologics. Dupilumab efficacy has been demonstrated in patients with baseline eosinophils ≥ 150 cells/μL. To avoid confusion, we suggest that, when presenting data within certain patient populations, the agency use biomarker cut-offs rather than phenotype terminology so that the reader is aware of which patient population is being discussed.</p> <p>Recommendation: Throughout the text, when discussing subpopulations within dupilumab data please use terminology such as eosinophils ≥ 150 cells/μL, or eosinophils ≥ 300 cells/μL.</p>
8	Outcomes of daily symptoms and quality of life and AAER in the subgroup of patients with eosinophilic asthma are available from the QUEST trial but not the unnamed phase 2b trial	<p>Comment: The data for the phase 2b trial has been published for the overall population as well as 325 patients with baseline blood eosinophils ≥ 300 cells/μL. This includes an LS mean change in ACQ-5 from baseline to week 24 of -0.42 (P=0.0171) and -0.55 (P=0.0021) in the 200 mg q2w and 300 mg q2w groups, respectively.</p> <p>Recommendation: Please refer to the subgroup of patients with “eosinophilic asthma” as the subgroup of patients with blood eosinophils ≥ 150 cells/μL or include the results for the subgroup of patients with blood eosinophils ≥ 300 cells/μL as detailed above.</p>
8	Across the phase 2b trial and QUEST, as described in ICER’s 2018 report and looking at patients across all eosinophil levels, the mean improvements in ACQ and AQLQ were greater with dupilumab 200 mg than with placebo (diff 0.39, 95% CI 0.25 to 0.53 and 0.29, CI 0.15 to 0.44, respectively), but smaller than the MCID.	<p>Comment: Please note, the change from baseline for the overall dupilumab 200mg q2w (-1.49), 300mg q2w (-1.45) and the placebo (-1.14) populations exceeded the MCID for ACQ-5. The MCID concept is meant to compare a change from baseline in an individual patient (or group of patients), not the difference in response between two populations.</p> <p>Recommendation: Delete “but smaller than MCID”.</p>
9	In VENTURE, the reduction in OCS dose was greater with dupilumab than with placebo (70% vs 42%; p<0.001). More patients treated with dupilumab also had a reduction from baseline OCS dose of at least 50% (80% vs. 50%; p<0.001)	<p>Recommendation: Please note that this occurred regardless of baseline Type 2 biomarker.</p>

	and had a reduction in OCS dose to less than 5 mg/day (69% vs. 33%).	
D19	In the Phase 2b trial at week 24, a statistically significant improvement in Pre-BD FEV ₁ was seen versus placebo in both the 200 mg dose (16.6L vs. 7.0; diff 9.6, CI 4.5, 14.7; P=0.0003) and the 300 mg dose dupilumab arms (17.3 vs. 7.0; diff 10.3, CI 5.3, 15.4; P<0.0001)	<p>Comment: The primary endpoint for this trial was LS mean change from baseline in FEV₁ at week 12 vs PBO in the population with blood eosinophils ≥ 300 cells/μl, and this was 0.26 (0.11, 0.40) P=0.0008 for the 200mg q2w group and 0.21 (0.06, 0.36) for the 300mg q2w group. It appears there may be a transcription error here as the units are incorrect</p> <p>Recommendation: For the overall population the results are 200 mg q2w: 0.29 (0.03) and 0.16 (0.07-0.24) L vs PBO for 300 mg q2w: 0.28 (0.03) and 0.16 (0.07-0.24) vs PBO.</p> <p>Please update the text: A statistically significant LS mean difference versus placebo in preBD FEV₁ was seen in the overall population for both the 200mg q2w dose (0.200 (0.11,0.28) L, p<0.0001) and the 300mg q2w dose (0.16 (0.08,0.25), P=0.0002). In the population with baseline blood eosinophils ≥300 cells/ul, the LS mean difference versus placebo in preBD FEV₁ was 0.26 (0.11,0.40) L, P=0.0008 for the 200mg q2w dose and 0.21 (0.06,0.36), P=0.0063, for the 300mg q2w dose.</p>
D19	In patients with EOS ≥300 at baseline, high dose dupilumab had the greatest improvement in Pre-BD FEV ₁ versus matched placebo (0.47 vs. 0.22; diff 0.24; CI: 0.16 to 0.32; P<0.001) compared to low dose versus matched placebo (0.43 vs. 0.21; diff 0.21; CI: 0.13 to 0.29).	<p>Comment: Please note that in the pivotal LIBERTY ASTHMA QUEST trial, efficacy was evaluated in two dose levels, however the magnitude of effect was not directly compared between the two doses. This study was not powered to detect differences between these two doses and would therefore suggest refraining from making qualitative comparisons.</p> <p>Recommendation: Please revise text as follows: In patients with blood eosinophils ≥300 at baseline, both doses of dupilumab significantly improved Pre-BD FEV₁ versus matched placebo: 300 mg q2w (0.47 vs. 0.22; diff 0.24; CI: 0.16 to 0.32; P<0.001) and 200 mg q2w (0.43 vs. 0.21; diff 0.21; CI: 0.13 to 0.29).</p>
D20	In LIBERTY ASTHMA VENTURE, a greater percentage of patients taking high dose dupilumab achieved a ≥ 90% reduction in oral glucocorticoid dose at 24 weeks (55.3% vs. 30.8%). High dose dupilumab also had a greater percentage of patients achieve ≥75% (68.9% vs. 39.3%), ≥ 50% (79.6% vs. 53.3%) and ≥ 0% (86.4% vs. 68.2%).	<p>Recommendation: Please refer to 300mg q2w dupilumab rather than “high dose.” Please also note the proportion of patients no longer requiring oral glucocorticoids at week 24 was 48% vs 25% with OR vs PBO of 2.74.</p>
D20	In a post hoc analysis of the phase 3 QUEST study, patients across the high	<p>Recommendation:</p>

	type 2 biomarker subgroups (defined as patients with elevated biomarkers) had lower AAER (range: 0.16 to 0.65) compared to placebo (range: 0.86 to 2.35).	Please be specific about which “high type 2 biomarker subgroups” are referred to here: patients with baseline blood eosinophils ≥ 150 cells/ μ l, blood eosinophils ≥ 300 cells/ μ l, or baseline FeNO ≥ 25 ppb.
D20	Patients with FeNO ≥ 25 and EOS ≥ 150 at baseline had a greater benefit in pre-BD FEV1 than the overall population versus matched placebo in high dose (diff 0.33; CI: 0.24 to 0.43) and low dose (diff 0.26; CI: 0.17 to 0.35) arms	<p>Comment: The effect sizes are reversed: with patients with both eosinophils ≥ 150 cells/μl and FeNO ≥ 25 ppb at baseline showing an LS mean difference versus placebo of 0.33 L (95% CI 0.24–0.43 L) and 0.26 L (95% CI 0.17–0.35 L) at week 52 when treated with dupilumab 200 mg or 300 mg every 2 weeks, respectively; further this data point seems out of context.</p> <p>Recommendation: Please highlight that dupilumab led to lung function improvements across all populations identified by baseline type 2 inflammatory biomarkers (EOS ≥ 150 cells/μl, EOS ≥ 300 cells/μl, or FeNO ≥ 25 ppb).</p>
D21	Patients in QUEST who did not meet the criteria for allergic asthma saw similar reductions across both doses versus placebo (overall: 60% and 45%; EOS ≤ 150 : 71% and 63%; ≥ 300 : 75% and 71%)	<p>Recommendation: Please use “EOS ≥ 150 cells/μl” instead of “EOS ≤ 150”.</p>

We appreciate the opportunity to be involved in this review and look forward to a continued dialogue with ICER.



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¹ DUPIXENT® (dupilumab) prescribing information. Tarrytown, NY, USA: Regeneron Pharmaceuticals, Inc.; January 2021.

² Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15(1):35-50

³ Buhl R, Korn S, Menzies-Gow A, et al. Prospective, single-arm, longitudinal study of biomarkers in real-world patients with severe asthma. *J Allergy Clin Immunol Pract.* 2020;8(8):2630-2639.e6

⁴ Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021.

⁵ Le Floch A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4R α antibody, is required to broadly inhibit type 2 inflammation. *Allergy.* 2020;75(5):1188-1204.

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- ⁶ Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med*. 2018;378(26):2486-2496. doi:10.1056/NEJMoa1804092
- ⁷ Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab Efficacy and Safety in Children with Uncontrolled, Moderate-to-Severe Asthma: The Phase 3 VOYAGE Study. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ⁸ Corren J, Castro M, O'Riordan T, et al. Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526. doi:10.1016/j.jaip.2019.08.050
- ⁹ Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention.2021.
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- ¹¹ Wechsler ME, Ford LB, Maspero JF, et al. Dupilumab Long-Term Safety and Efficacy in Patients With Asthma: LIBERTY ASTHMA TRAVERSE. Presented at the 30th International Congress of the European Respiratory Society (ERS); Virtual Congress; September 7-9, 2020.
- ¹² Wechsler ME, Ford LB, Maspero JF, et al. Dupilumab Shows Sustained Efficacy and Improvements in Asthma Control and Health-Related Quality of Life in Patients With Moderate-to-Severe Asthma: LIBERTY ASTHMA TRAVERSE. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ¹³ Wechsler ME, Pavord ID, Papi A, et al. Long-Term Dupilumab Treatment in Moderate-to-Severe Asthma With Type 2 Inflammation: Open-Label LIBERTY ASTHMA TRAVERSE Study. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ¹⁴ Hanania NA, Dorscheid DR, Bourdin A, et al. Long-term Exacerbations and Lung Function Assessment in LIBERTY ASTHMA TRAVERSE Stratified by Lung Function Improvements at the End of Parent Study. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ¹⁵ Papi A, Bourdin A, Watz H, et al. Long-Term 3-Year Efficacy of Dupilumab in QUEST Patients Enrolled in LIBERTY ASTHMA TRAVERSE. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ¹⁶ Sher LD, Wechsler ME, Rabe KF, et al. Assessment of Long-Term Maintenance of OCS Reduction and Efficacy in the Dupilumab LIBERTY ASTHMA TRAVERSE Extension Study. Presented at the 2021 ATS International Conferences, May 14-19, 2021.
- ¹⁷ Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *The Lancet Respiratory Medicine* (published online ahead of print 28 September 2021) [https://doi.org/10.1016/S2213-2600\(21\)00322-2](https://doi.org/10.1016/S2213-2600(21)00322-2)
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²⁸ Sher LD, Wechsler ME, Rabe KF, et al. Assessment of Long-Term Maintenance of OCS Reduction and Efficacy in the Dupilumab LIBERTY ASTHMA TRAVERSE Extension Study. Presented at the 2021 ATS International Conferences, May 14-19, 2021.

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