

On behalf of the Asthma and Allergy Foundation of America (“AAFA”), the American Academy of Allergy, Asthma & Immunology (“AAAAI”) and the Allergy & Asthma Network (“AAN”), we would like to thank the Institute for Clinical and Economic Review (“ICER”) for the opportunity to comment on ICER’s Draft Scoping Document on the comparative clinical cost effectiveness and value of tezepelumab for the treatment of severe asthma. We appreciate ICER’s ongoing willingness to engage with us and to better understand patients’ perspectives.

Because of the major racial and ethnic disparities in the burden of asthma in the U.S., we are writing today to specifically urge ICER to use this review as an opportunity to identify and address the ways in which the data informing its analyses may reflect and even perpetuate biases in the healthcare and clinical trial systems. Our concerns are outlined below.

### Asthma Disparities in the U.S.

AAFA has worked to address disparities in asthma prevalence and care for years. In AAFA’s recent report *Asthma Disparities in America: A Roadmap to Reducing the Burden on Racial and Ethnic Minorities*,<sup>i</sup> we detailed the serious and persistent racial and ethnic disparities in the burden of illness, including:

- Non-Hispanic Black Americans are almost three times as likely to die from asthma-related causes than non-Hispanic whites.<sup>ii</sup>
- Black children under age 15 die from asthma at a rate ten times higher than non-Hispanic white children.<sup>iii</sup>
- Black women are 20% more likely to have asthma than non-Hispanic white women.<sup>iv</sup>
- Children with asthma who belong to racial or ethnic minority communities have higher rates of hospitalization, more visits to emergency rooms, and higher mortality rates from asthma than white children.<sup>v</sup>

As discussed in the report, the disparate burdens of asthma in the U.S. are rooted in deep structural inequities, including racism, that contribute to individual and community risk and access to care.<sup>vi</sup> Asthma disparities are exacerbated by social determinants that negatively impact health and wellbeing including poverty, lack of access to quality education or employment, unhealthy housing, unfavorable work or neighborhood conditions, exposure to neighborhood violence, and the clustering of poverty in particular groups of people and in particular places.

### Equity in Clinical Trials

We are particularly concerned that the underrepresentation of racial and ethnic minority populations in clinical studies – despite the higher burden of asthma they experience – creates a systematic bias in the data on which ICER relies.

As you are aware, AAFA has joined with other organizations in the past expressing concern about ICER's reliance on QALYs.<sup>vii</sup> An overarching concern is that metrics depend on averages across what may be highly heterogeneous patient populations – within which people may differ considerably in their experience of the disease and what factors they value in assessing their own quality of life. Furthermore, QALYs devalue the lives of people with chronic conditions and other disabilities compared to those considered to be in objectively “perfect” health. The use of evLYGs can mitigate some of the quality of life concerns, but still fails to capture the range of clinical and personal experiences of disease, and of treatment, across patient populations.

AAFA's work on disparities in asthma underscore the further concern of the underlying underrepresentation of racial and ethnic minorities in clinical trials. In clinical research in the U.S., racial and ethnic minorities are broadly underrepresented. For example, from 1993-2013, only 1.9% of all studies of respiratory disease (and less than 5% of NIH-funded studies) formally reported inclusion of racial or ethnic minority subjects.<sup>viii</sup> Therefore, most cost-effectiveness analyses, including those used to estimate cost per QALY, rely on data from clinical trials that disproportionately focus on Caucasian participants.

As the National Minority Quality Forum (NMQF) has described, this pattern means that the data informing cost effectiveness assessments “compromises the clinical validity of data and information regarding disease presentation and therapeutic responses and findings regarding safety and efficacy.”<sup>ix</sup> For a given analysis, this results in a lack of meaningful information on which to develop an understanding of how a disease, and treatment, may affect racial and ethnic minorities. In the aggregate, the pattern creates a systematic bias that favors medications that are more effective for Caucasians and disfavors those that effective for minority populations. As NMQF explains:

For example, if a particular therapy is effective for an African American population, but less effective for a Caucasian population, but the enrolled trial cohort is dominantly Caucasian, with African Americans under-represented, its average effect size demonstrated by the RCT will be small, and the therapy will have a lower chance of being approved.

Conversely, if a therapy is highly effective for Caucasians and less effective for African Americans, with a similar distribution of RCT participants as before, this will result in an overestimation of the effect size and increase its chance of being approved. Multiply this effect by the hundreds and thousands of trials that have evaluated the thousands of therapies that have been approved – or not – over the decades and you have a systematic bias of available therapies that favor Caucasians to the detriment of African Americans and other disenfranchised patients and communities.<sup>x</sup>

This distortion of the data extends to cost-effectiveness analyses, which can impact payers' willingness to cover certain drugs, thereby conditioning access on racially nonrepresentative data.

### Recommendations

The challenge of increasing representation of racial and ethnic minorities in clinical trials is longstanding and complex. As AAFA detailed in our disparities report, major steps are needed on the part of funders, industry, and academic institutions to increase representation of Black, Hispanic, and Indigenous people in clinical trials for asthma and other respiratory diseases.<sup>xi</sup>

While we do not expect ICER to solve this problem, we believe it is time for ICER to more explicitly acknowledge the impact of underrepresentation in clinical trials on the entirety of the evidence that informs ICER's analyses. To that end, because of the major and unacceptable disparities in asthma prevalence and care, we urge ICER to use the tezepelumab review as an opportunity to start analyzing and reporting on key issues related to equity in trial data. Black Americans are three times more likely to die from asthma than white Americans. Black Americans are also five times more likely treated for asthma in hospital emergency rooms compared to white patients.<sup>xii</sup> We encourage ICER to consider and report on information such as:

- The extent to which racial and ethnic minority populations were represented in each of the clinical trials used to inform ICER's analysis;
- Whether the data are sufficient to provide effectiveness and cost-effectiveness analyses by racial or ethnic group;
  - If the data are sufficient, whether it is feasible to develop weighted estimates that would reflect outcomes if racial and ethnic minorities were proportionately represented in the clinical trials;
  - If the data are not sufficient, what gaps this creates in understanding of the effectiveness, and cost-effectiveness, of the treatment for different populations;
- Whether disparities in the burden of a given disease mean that an "average" effectiveness has different implications for different groups. For example, if Black adults are more likely to be hospitalized for a given disease, does a drug showing reductions in hospitalization rates mean that it would be particularly important for Black populations?

This level of engaging with the data is crucial if ICER intends to meaningfully address equity in this, and future, analyses.

### Conclusion

Thank you very much for your time and attention. We look forward to continuing to work with ICER to reflect the diverse patient experience among those with asthma, and to begin to address the impact of the systematic racial biases that affect healthcare and clinical trials.

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

<sup>ii</sup> *Id.*

<sup>iii</sup> Office of Minority Health. Asthma and African Americans. U.S. Department of Health and Human Services. Available at: <https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=15>

<sup>iv</sup> *Id.*

<sup>v</sup> Anna Volerman, Marshall H. Chin and Valerie G. Press. Solutions for Asthma Disparities. *Pediatrics* March 2017, 139 (3) e20162546; DOI: <https://doi.org/10.1542/peds.2016-2546>

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

<sup>vii</sup> Letter from Patient Groups to Dr. Steven Pearson regarding ICER 2020 Value Assessment Framework (October 19, 2019). Available at <https://www.aafa.org/media/2497/aafa-sign-on-letter-icer-proposed-updates-2020-value-assessment-framework.pdf>

<sup>viii</sup> Burchard EG, Oh SS, Foreman MG, Celedón JC. Moving toward true inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. *Am J Respir Crit Care Med.* 2015 Mar 1;191(5):514-21. doi: 10.1164/rccm.201410-1944PP. PMID: 25584658; PMCID: PMC4384771.

<sup>ix</sup> National Minority Quality Forum, “Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities White Paper.” Available at <https://www.nmqf.org/nmqf-media/traditional-value-assessment-methods>

<sup>x</sup> *Id.*

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

<sup>xii</sup> *Id.*

## SUMMARY

Amgen and AstraZeneca appreciate the opportunity to comment on ICER's *Draft Background and Scoping Document for Tezepelumab for Severe Asthma*. Approximately 5 to 10% of asthma patients have severe asthma, and many remain uncontrolled despite the use of high-dose inhaled corticosteroids (ICS) and an additional controller such as long-acting beta-agonists (LABA) or oral corticosteroids (OCS).<sup>1,2</sup> Tezepelumab is the only biologic medicine to consistently and significantly reduce annualized asthma exacerbation rates (AAER) in severe uncontrolled asthma patients regardless of baseline blood eosinophil counts (BEC) across Phase II and Phase III clinical trials.<sup>3,4,5,6,7</sup> Improvements in AAER with tezepelumab have also been consistent irrespective of allergic status and fractional exhaled nitric oxide. Amgen and AstraZeneca are committed to helping patients living with severe asthma, and we would like to highlight important recommendations for ICER's assessment:

- 1. Include all FDA-approved biologics as comparators in this assessment, including reslizumab, mepolizumab, and benralizumab. Align comparison to other biologics, with demonstrated efficacy of these biologics based on blood eosinophil counts or allergic status.**
- 2. Focus on AAER as a primary endpoint for severe asthma patients; also compare exacerbations leading to ER visits and hospitalizations.**
- 3. To provide an overall efficacy estimate for tezepelumab-specific outcome measures, pool or meta-analyze two relevant pivotal randomized controlled trials - NAVIGATOR and PATHWAY.**
- 4. Incorporate real-world data (RWD) into the economic analysis to increase generalizability in baseline exacerbation rates, distribution of exacerbation events, and real-world OCS use.**
- 5. Estimate budget impact by using the uptake of other biologics for severe asthma patients as a guide to estimating the number of patients that will receive tezepelumab.** ICER should include the proportion of patients who are not eligible for current biologics (BEC < 150 cells/ $\mu$ L and non-allergic) who represent the patients who will be incrementally eligible for tezepelumab.

## RECOMMENDATIONS

- 1. Include all FDA-approved biologics as comparators in this assessment, including reslizumab, mepolizumab, and benralizumab. Align comparison to other biologics, with demonstrated efficacy of these biologics based on blood eosinophil counts or allergic status.**

**The Draft Scoping Document only lists omalizumab and dupilumab as comparators.** While omalizumab is an appropriate (and the only) comparator for allergic asthma, dupilumab is not representative of Anti-IL-5's/Anti-IL-5R $\alpha$ . We recommend that ICER incorporate all Anti-IL-5's/Anti-IL-5R $\alpha$  as comparators as each is clinically different with variations in clinical evidence, dosing regimens, and mechanisms of action. Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway, whereas dupilumab inhibits the IL-4R $\alpha$  subunit shared by both IL-4 and IL-13, thus inhibiting both IL-4 and IL-13 signaling. ICER's 2018 report demonstrates this variability, recognizing that there is significant heterogeneity between the drugs in terms of: 1) scope of FDA indication, 2) exacerbation rates in trials, 3) average age of trial participants, 4) asthma severity, 5) definition of exacerbation, and 6) mean difference in Asthma Quality of Life Questionnaire / Asthma Control Questionnaire between treatment and placebo.<sup>8,9</sup> Table 1 summarizes the relevant information on the approved biologics.

**If looking at eosinophilic subgroups, ICER should ensure that the BEC for these subgroups closely aligns with the pivotal study design and eligibility criteria of other biologics.** Specifically, these subgroups are patients with 1) BEC  $\geq$  150 cells/ $\mu$ L (mepolizumab and dupilumab) and 2) BEC  $\geq$  300 cells/ $\mu$ L (benralizumab).

**For comparisons with other biologics, the background SoC needs to reflect the current SoC for patients.**<sup>10</sup> Many earlier omalizumab studies used a definition of SoC that differs from both ICER's scoping document (inhaled corticosteroid therapy and at least one additional controller medication) and the SoC in more recent biologics studies.<sup>11</sup>

**Finally, we further note that any assessment of efficacy among adolescents must be considered with caution due to the small sample size for this age group.**

## **2. Focus on AAER as a primary endpoint for severe asthma patients; also compare exacerbations leading to ER visits and hospitalizations.**

**AAER is an objective assessment of disease severity.** As the primary endpoint in the PATHWAY and NAVIGATOR trials, AAER is patient-relevant and drives other patient-relevant endpoints, including patient-reported outcomes (PROs). AAER is also important for ICER's cost-effectiveness model as it determines costs, the proportion of patients in a given disease state, and QALYs. Given that AAER is the primary endpoint, it should be the focus of indirect treatment comparisons (ITCs) with other biologics appropriately aligned to BEC. Other relevant endpoints, such as FEV1, could also be considered in ICER's ITC if sufficient evidence is available.

**In addition to AAER and FEV1, ICER should also capture serious exacerbations (defined as at least one hospitalization, intensive care unit stay, or mechanical ventilation).**<sup>12</sup> ICER's last assessment report did not include serious exacerbations in its clinical assessment.<sup>13</sup> Data on efficacy against serious exacerbations should be an essential part of ICER's assessment. There is evidence of differential effect across biologics on these more severe endpoints, which are also relevant drivers of healthcare costs. Hence, this assessment should capture evidence of differential effect across biologics on these more severe endpoints.

## **3. To provide an overall efficacy estimate for tezepelumab-specific outcome measures, pool or meta-analyze two relevant pivotal randomized controlled trials - NAVIGATOR and PATHWAY.**

**PATHWAY and NAVIGATOR are relevant to the proposed population for evaluation, and both include AAER as the primary endpoint.**

**Data are available on OCS-dependent patients from SOURCE, NAVIGATOR, and PATHWAY.** While SOURCE captured AAER as a secondary endpoint, the trial population is distinct, focusing on a regimented OCS reduction in OCS-dependent patients. It is therefore not appropriate to combine SOURCE with the other trials. Additionally, due to the nature of reducing OCS during treatment – compared to NAVIGATOR and PATHWAY in which background medication is maintained constant – ICER should not use SOURCE for pooled analysis. Similarly, this assessment should separately analyze OCS reduction trials for other biologics.

**If ICER assesses reduction of maintenance OCS as an endpoint, SOURCE is relevant.** For a more thorough discussion of SOURCE, please see the presentations at the 2021 American Thoracic Society (ATS) Conference.

<sup>14,15</sup> Of note, SOURCE had a large placebo response, and there were differences between SOURCE's trial design and other studies of biologics. SOURCE allowed patients multiple opportunities for OCS dose reductions in a longer trial period (48 weeks versus a shorter evaluation period of 24 weeks). Notably, in the PATHWAY and NAVIGATOR studies, approximately 9% of enrolled subjects were OCS-dependent.<sup>16</sup> In those patients, tezepelumab was associated with numerically fewer asthma exacerbations and improvements in lung function and asthma control. A recent presentation from ATS 2021 includes more details on these data.<sup>17</sup> The proportion of patients with OCS-dependence in PATHWAY and NAVIGATOR is similar to what was observed in a large, contemporary, real-world cohort of U.S. specialist-treated patients with severe asthma, which specifically was 12% of patients in the CHRONICLE Study.<sup>18</sup>

#### **4. Incorporate RWD into the economic analysis to increase generalizability in baseline exacerbation rates, distribution of exacerbation events, real-world discontinuation, and real-world OCS use.**

**Baseline exacerbation rates that reflect real-world pre-biologic rates should be in ICER'S base case.** The baseline AAER for the NAVIGATOR study was 2.1 exacerbations per patient per year. As shown in Table 2, RWD supports these rates, with several studies reporting baseline rates for severe asthma of approximately 2 per patient per year. Importantly, exacerbation rates for scenario analysis in, for example, inner-city residents should be higher than the 2.1 exacerbations for the wider severe asthma population.

**Considering the treatment costs for this assessment, ICER should include real-world persistence rates to account for discontinuation.** To estimate persistence, we recommend ICER apply RWD on persistence using other biologics as analogs.

**Include real-world data on OCS use in the base case.** The annual prevalence for long-term OCS use ranges from 6.5% for mild asthma to 10% for those with severe asthma.<sup>19</sup>

#### **5. Estimate budget impact by using the uptake of other biologics for severe asthma patients as a guide to estimating the number of patients that will receive tezepelumab.** ICER should include the proportion of patients who are not eligible for current biologics (BEC < 150 cells/ $\mu$ L and non-allergic) who represent the patients who will be incrementally eligible for tezepelumab.

**Only patients who have BEC < 150 cells/ $\mu$ L and are non-allergic will be newly eligible for biologic treatment following approval of tezepelumab in its expected FDA indication.** Most severe uncontrolled asthma patients are already eligible for one or more of the currently available biologic therapies. The additional subgroup (BEC < 150 cells/ $\mu$ L and non-allergic) is only 15% of all U.S. severe asthma patients.<sup>20</sup> In 2018, ICER's assessment estimated 27% of severe asthma patients were taking any biologic, including all biologics approved at the time.<sup>21</sup>

## **CONCLUSION**

We appreciate ICER's consideration of new treatments in this devastating disease and look forward to working with ICER in this assessment. To ensure greater alignment and generalizability to the decision problems payers face, this assessment should include all FDA-approved comparators in the comparative clinical benefit, appropriate BEC cut-offs and IgE/positive allergen tests, use real-world baseline exacerbation rates, and look to analogs from other biologics to guide budget impact.

**Table 1: Tezepelumab Comparators for ICER’s Comparative Clinical Benefit Assessment<sup>22</sup>**

| Drug                                    | Dosing <sup>23</sup>                                    | Mechanism <sup>24</sup> | FDA Indication <sup>25</sup>  | Comparative Clinical Benefit <sup>26</sup> | Trial Inclusion BEC & Eligibility Criteria <sup>27</sup>   |
|---|---|-------------------------|---|--|--|
| Omalizumab (Xolair®, Genentech)         | weight-based SC Q 2-4 weeks*                            | Anti-IgE                | Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens                        | B  | Not required for trial inclusion, though different rate ratios for <300 and >300. Eligibility BEC: Any   |
| Mepolizumab (Nucala®, GlaxoSmithKline)  | 100 mg SC Q 4 weeks*                                    | Anti-IL-5               | Age ≥ 12 years with severe asthma and eosinophilic phenotype [Age ≥ six years as of 2020]                                 | B  | ≥150 at initiation or ≥300 in past 12 months. Eligibility BEC: ≥150 cells/μl   |
| Reslizumab (Cinqair®, Teva)             | 3 mg/kg IV Q 4 weeks*                                   | Anti-IL-5               | Age ≥ 18 years with severe asthma and eosinophilic phenotype  | C+   | ≥400. Eligibility BEC: ≥ 400 cells/μl  |
| Benralizumab (Fasenra™, AstraZeneca)    | 30 mg SC Q 4 weeks x 3, then Q 8 weeks*                 | Anti-IL-5Rα             | Age ≥ 12 years with severe asthma and eosinophilic phenotype  | C+   | Any (stratified < vs. ≥300 at enrolment). Eligibility BEC: ≥ 150-300 cells/μl  |
| Dupilumab (Dupixent®, Sanofi/Regeneron) | 200 mg SC Q 2 weeks<br>300 mg SC Q 2 weeks <sup>‡</sup> | Anti-IL-4Rα             | Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma | C+   | Any (690/1638 patients with ≥300). Eligibility BEC: ≥ 150 cells/μl [No efficacy demonstrated in EOS <150 cells/μl]; Eligibility BEC [OCS dependent]: Any |

\* Health Care Professional Required for administration; ‡ Self-administered

**Table 2: Review of Studies Capture Baseline Asthma Exacerbation Rates**

| Authors<br>(Year)  | Population   | Average Exacerbation  |
|--|--|---|
| <b>BASELINE EXACERBATION RATE (number per patient-year)</b>                                  |  |   |
| <p><b>Soong et al. (2020)</b><br/><i>(draft manuscript can be provided upon request)</i></p> | <p><b>Study:</b> Ongoing observational study of U.S. adults with severe asthma<br/> <b>Location:</b> US<br/> <b>N=</b> 1884<br/> <b>Mean Age:</b> 55 years<br/> <b>Population:</b> Adults ≥18 years old, with a severe asthma diagnosis receiving 1) FDA-approved monoclonal antibody therapy, 2) maintenance systemic corticosteroids (mSCS) or other systemic immunosuppressants for ≥50% of the prior 12 months or 3) adults with uncontrolled asthma treated w/ high doses ICS and additional controllers.</p> | <p><b>Exacerbation Rates Before Biologic Starting/Switching</b><br/> <b>Starting biologics: 1.7</b></p> <ul style="list-style-type: none"> <li>• Starting anti-IgE: 1.6</li> <li>• Starting biologics other than anti-IgE: 1.8</li> <li>• Switching between any two biologics: 1.6</li> </ul>   |
| <p><b>Llanos et al. (2020)</b><br/><a href="#">Link</a></p>                                  | <p><b>Study:</b> Retrospective cohort, claims analysis<br/> <b>Location:</b> US<br/> <b>N=</b> 346<br/> <b>Mean Age:</b> 49.3 years<br/> <b>Population:</b> Patients ≥12 years old, with an asthma diagnosis and a medical/pharmacy claim between Nov 1, 2015-March 31, 2017 that included a drug code indicating administration of mepolizumab (MEPO).<sup>28</sup></p>   | <p><b>12 Month Before Mepolizumab Initiation</b><br/> All exacerbation: 292 (84.3%)<br/> <b>Rate of exacerbation: 2.68</b><br/> Exacerbations requiring hospitalizations: 26 (7.51%)<br/> Rate of exacerbation: 0.11<br/> <u>N-141 (Clinical trial-like sub-cohort)</u><br/> All exacerbation: 141 (100%)<br/> Rate of exacerbation: 3.97<br/> Exacerbations requiring hospitalizations: 0.15</p> |
| <p><b>Abbas et al. (2020)</b><br/><a href="#">Link</a></p>                                   | <p><b>Study:</b> Retrospective cohort<br/> <b>Location:</b> US<br/> <b>N=</b> 99<br/> <b>Mean Age:</b> 58 years<br/> <b>Population:</b> Adult patients enrolled in severe asthma biologic program at Mary Parkes Center for Asthma between Jan 2014- Aug 2019.<sup>29</sup></p>  | <p><b>Before/After Biologic Add-on Therapy</b><br/> <b>Reduction in exacerbation rates: 57% (4.65 vs. 2.0)</b><br/> Average dose of maintenance oral corticosteroids: 30% (12.8 vs. 9 mg)<br/> Subgroup (patients who switched from another biologic due to partial/no response) mean reduction in exacerbation rates: 38% (3.5 vs. 2.17)</p>   |
| <p><b>Voelker D et al. (2019)</b><br/><a href="#">Link</a></p>                               | <p><b>Study:</b> Retrospective chart review of electronic medical records<br/> <b>Location:</b> US<br/> <b>N=</b> 50<br/> <b>Mean Age:</b> 54 years<br/> <b>Population:</b> Patients with severe asthma who underwent biologic pharmacotherapy at Mayo Clinic in Rochester, Minnesota, between Jan 2016 and Dec 2018</p>   | <p><b>12 Month before drug initiation</b><br/> <b>Median number of asthma EXA: 4 (8%)</b></p>   |

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- <sup>9</sup> In addition, ICER's panel voted omalizumab and mepolizumab as high certainty of an incremental net health benefit. In contrast, it gave reslizumab, benralizumab, and dupilumab a moderate certainty of a net health benefit comparable to or better than the standard of care.
- <sup>10</sup> The SoC medication allowed in tezepelumab trials (ICS/LABA/long-acting muscarinic antagonists (LAMA)/ leukotriene receptor antagonists (LTRA)) reflect commonly used non-biologic treatments in severe uncontrolled asthma (*e.g.*, per GINA step 4-5).
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- <sup>29</sup> Comparison was made with patient's own pre-biologic therapy data in the preceding 12 months.

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Boston, MA 02109**

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the invitation to provide comments on the *Tezepelumab for Severe Asthma: Effectiveness and Value Draft Scope*.<sup>1</sup> In the U.S., Genentech and Novartis Pharmaceuticals Corporation work together to develop and co-promote Xolair® (omalizumab). Xolair was the first FDA-approved biologic for allergic asthma in 2003; it is indicated for moderate to severe persistent asthma for patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.<sup>2</sup> An abundance of Xolair data currently exists; there is more than 18 years of real-world experience and over 1.3 million patient-years of exposure.<sup>3</sup>

Anchoring on our participation in and experience with the previous 2018 ICER review,<sup>4</sup> we highlight three recommendations for this assessment:

- 1. Do not compare asthma biologics to each other in both the clinical and economic evaluations due to heterogeneity in the following parameters: study designs, disease severity, asthma phenotype, inclusion criteria, and outcome measurements**
- 2. Supplement randomized-controlled trial data with available real-world evidence to augment the level of confidence provided by the body of evidence and the magnitude of the net health benefit in the ICER evidence ratings**
- 3. Include population-specific analyses in the clinical and economic evaluations across race, ethnicity, gender, socio-economic status, and region; this enables appropriate recognition of patients who disproportionately suffer from asthma-related consequences**

We further expand on these recommendations with rationale and supporting references below.

**1. Recommendation: Do not compare asthma biologics to each other in both the clinical and economic evaluations due to heterogeneity in the following parameters: study designs, disease severity, asthma phenotype, inclusion criteria, and outcome measurements**

*Rationale:* Asthma biologics' clinical development programs are informed by clinical practice guidelines and understanding of the disease at the time of trial execution, with both evolving over time. The pivotal trials for Xolair, including study design, trial populations, asthma concomitant medications, and measurement of exacerbations were informed by the 1997 *National Heart, Lung, and Blood Institute (NHLBI) Asthma* guidelines,<sup>5</sup> whereas more recent asthma biologic trials use 2007 *NHLBI Asthma* and

*Global Initiative for Asthma (GINA)* guidelines to design trials, which differ significantly.<sup>6,7</sup> This renders the comparison of the efficacy and safety of Xolair to subsequently approved biologics invalid.

Asthma is a complex and heterogeneous disease, with distinct phenotypes. Specific to allergic asthma, Xolair is the only FDA-approved product included in this review that is indicated for patients 6 years and older with a confirmed allergic phenotype.<sup>2</sup> In the pivotal studies, study participants were explicitly selected based on their allergic asthma status by requiring a positive skin-prick test for at least one perennial aeroallergen.<sup>8-10</sup> Tezepelumab trials,<sup>11-13</sup> did not have an inclusion criteria for allergic asthma.

Other important trial differences are also noteworthy, and make comparisons between Xolair and tezepelumab invalid. Tezepelumab pivotal trials selected for exacerbation history, which resulted in an enriched, exacerbation-prone and more severe asthma patient population, compared to the Xolair pivotal study population.<sup>8-13</sup> Additionally, asthma exacerbations were assessed at different time points and defined differently between the studies. A comparison of the reported outcomes from dissimilar study populations can lead to bias and uncertainty, in addition to violating the transitivity and homogeneity assumptions necessary for conducting a network meta-analysis.

*Implications:* Inconsistencies across the pivotal trials, varying definitions of the primary endpoint, and imbalanced distribution of effect modifiers would render direct and indirect treatment comparisons of asthma biologics as inconclusive and uncertain. As a result, healthcare decision makers may incorrectly interpret the findings that could negatively impact patient access to valuable therapies.

## **2. Recommendation: Supplement randomized-controlled trial data with available real-world evidence to augment the level of confidence provided by the body of evidence and the magnitude of the net health benefit in the ICER evidence ratings**

*Rationale:* In the 2018 report, ICER, in collaboration with *Asthma and Allergy Foundation of America*, highlighted outcomes important to patients beyond reduction in asthma exacerbations, such as symptom relief, asthma control, reduction in steroid use, and impact on work/school.<sup>4</sup> Genentech is committed to generating real-world evidence on these outcomes that ICER highlighted.<sup>14</sup>

There is now a large body of evidence for Xolair that extends from high-quality, long-term efficacy and safety data, as demonstrated in randomized-controlled trials (RCTs), to post-marketing safety and pragmatic observational studies, representing a real-world patient population. Long-term safety studies have shown that Xolair is well-tolerated and not associated with an increase in incidence of adverse events in adults, children, and in-utero exposure.<sup>2,15</sup> Moreover, recently generated evidence from 86 observational/open-label studies conducted over 13 years concluded that treatment with Xolair is associated with improvements in patient-relevant outcomes such as lung function, asthma control, and reduction in severe exacerbations and healthcare resource utilization (HCRU).<sup>16</sup> Thus, real-world studies further complement and extend the efficacy and safety findings as well as patient-relevant outcomes that might not be fully captured in the controlled environment of the RCTs, and should be included in this review.

*Implications:* RCTs are not able to fully capture the patient-lived experience due to their short duration; real-world evidence can fill this gap by providing supplemental long-term information on treatment

benefits and potential harms. Therefore, it is important to include comprehensive body of evidence in the summary of clinical data and in the rating on long-term value to ensure a more robust value assessment of treatments in this complex landscape.

**3. Recommendation: Include population-specific analyses in the clinical and economic evaluations, across race, ethnicity, gender, socio-economic status, and region; this enables appropriate recognition of patients who disproportionately suffer from asthma-related consequences**

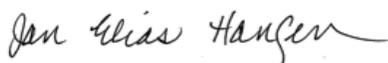
*Rationale:* Genentech appreciates ICER's plan to evaluate subgroups of patients with higher baseline severity for asthma and other potentially disadvantaged populations.<sup>1</sup> Genentech is committed to advancing the inclusion of underrepresented groups in research, development, and care delivery to enrich scientific insights and to improve equity in health and healthcare access. Xolair specifically has been studied in inner-city, low-income pediatric and young-adult patients, and has consistently demonstrated significant reductions in asthma symptoms and exacerbations.<sup>17, 18</sup>

In addition, while some populations such as children and pregnant women may not be included in the RCTs due to their stringent inclusion and exclusion criteria, this may not reflect clinical practice in real-world settings. A systematic review of efficacy and safety for Xolair-treated children and adolescent patients demonstrated significant reductions in annual exacerbations and symptoms, HCRU, and improved asthma control; additionally no new safety signals were identified.<sup>15</sup> Finally, EXPECT, a Xolair registry of treated pregnant individuals, found perinatal outcomes to be consistent with rates published in other studies.<sup>19</sup>

*Implications:* It is important to recognize that asthma is a heterogeneous condition which affects diverse populations. Evaluating additional patient populations that could benefit from asthma therapies, increases the representation, generalizability and applicability of the findings of this assessment, further impacting appropriate access to asthma treatments for a diverse, real-world population.

In summary, we believe incorporating the aforementioned recommendations will result in a more objective and robust assessment of the agents in this review. Asthma is a heterogeneous and chronic condition that requires a personalized and patient-centric approach to treatment, and it is important to preserve access to multiple therapeutic options for patients who need them. We are confident in the value of Xolair, as demonstrated by nearly two decades' of robust real-world experience. If helpful, we are open to sharing our clinical and health economics expertise in asthma through active engagement and collaboration with ICER for this review.

Sincerely,



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Genentech, US Medical Affairs

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