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June 5, 2018

Milon Waththuhewa, Pharm. D., M.Sc.
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Dr. Waththuhewa:

Thank you for the opportunity to review ICER's draft scoping document: Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation. A panel of ATS asthma experts has reviewed the draft scoping document and, in general, concurs with the draft PICO questions included in the document. However, the ATS does recommend that ICER include use of long-acting muscarinic antagonists (LAMAs) as another controller medication for patients with asthma. Adding LAMAs to list of controller medications patients may be using in the **Populations** section of the document would make that section more comprehensive. The following is our recommended edit:

"…(e.g., long-acting beta agonists, leukotriene agonists, theophylline, oral corticosteroids, and long-acting muscarinic antagonists)."

The ATS appreciates the opportunity to review the draft scoping document and looks forward to continuing to review and comment on ICER's review of monoclonal antibodies for the treatment of asthma.

Sincerely,

Polly Parsons, MD
President
American Thoracic Society

Asthma and Allergy Foundation of America

June 5, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted electronically to publiccomments@icer-review.org

To Whom It May Concern:

I am writing on behalf of the Asthma and Allergy Foundation of America (AAFA) to comment on the Draft Scoping Document on Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation. As the leading patient organization for people with asthma and allergies and the oldest asthma and allergy patient group in the world, AAFA appreciates the opportunity to offer insight into the experiences of patients with moderate to severe asthma. Our recent 2017 patient survey, "My Life With Asthma,"[1] a national, three-part study about asthma in the United States, offers qualitative insight on the benefits and harms not typically addressed with clinical evidence. What follows are our findings that we hope will provide greater insight as ICER does its assessment on biologic therapies for treatment associated with type 2 asthma.

Disease Experience: AAFA's survey included a total of 804 adult respondents living with asthma. Of these, 185 had "severe uncontrolled" asthma.[2] Among those with severe uncontrolled asthma, more than half of respondents reported that they experienced asthma symptoms more than once a day.[3] Over a quarter of other respondents have symptoms more than twice a week.[4] Respondents with severe uncontrolled asthma frequently end up in the emergency room. Eighteen percent reported one visit to the ER in the past 12 months, and an additional 42 percent reported two or more ER visits over the same time period.[5] Meanwhile, 28 percent of other respondents with asthma reported at least one ER visit in the past 12 months.[6]

Day-to-Day Life: The majority of those with severe uncontrolled asthma said they were scared and burdened by their condition.[7] More than two-thirds said it prevents them from living the life they want to live and more than three quarters said their asthma is always in the back of their

[1] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). The full report is available at www.aafa.org/media/my-life-with-asthma-in-2017-survey-findings-report.pdf.
[2] These respondents reported experiencing symptoms of asthma such as chest tightness, cough, shortness of breath, or wheezing more than two times per week; waking up during the night because of coughing or other asthma symptoms more than once per week; using a quick-relief or "rescue" inhaler more than two times per week; or having at least two asthma attacks that required them to take oral corticosteroids in the past 12 months. In addition, these 185 respondents reported either that a doctor or nurse had told them they had severe asthma, and that they had used a combination inhaler, an anti-IgE biologic agent, or an anti-IL-5 biologic agent in the past 12 months for their asthma.
[3] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 5.
[4] *Ibid*
[5] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 6.
[6] *Ibid*
[7] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 7.

mind.[8] Close to half (44 percent) felt like asthma ruins their life.[9] Other respondents were less likely to report similar day-to-day impacts of asthma on their lives, but significant portions were scared and burdened by their asthma, as well as prevented from living the life they want to live.[10]

Impact on Family and Caregivers: Sixty percent of those with severe uncontrolled asthma and 31 percent of others reported that their conditions scare their loved ones.[11] Almost half of respondents with severe uncontrolled asthma reported their condition was a burden to their family.[12] Among caregivers for those with severe asthma, 77% reported being scared by their charge's condition, as were 29 percent of the caregivers who care for others with asthma.[13]

Impact on Ability to Work, Exercise, Care for Family: Respondents with severe uncontrolled asthma were much more limited in their daily activities than others with asthma. Forty percent of respondents in the former category reported extreme limitations on their activities.[14] Nearly three quarters of respondents with severe uncontrolled asthma and half of other respondents missed at least one day of work in the past 12 months, and severe uncontrolled asthma was likely to cause extended absences from work (41 percent missed over 10 days of work).[15] When at work or school, a majority of respondents in both categories reported at least one day in the past 12 months when tasks were difficult to perform because of asthma.[16]

Treatments: Cost and Other Barriers: Respondents with severe uncontrolled asthma were generally less satisfied with current asthma medicines than other respondents. More than one in three in the former category reported being somewhat or very unsatisfied compared to only 14 percent of the latter.[17] Both types of respondents said treatment effectiveness and cost were the most important factors.[18]

Compliance with asthma treatment was similar across both groups: around one in four respondents always used their asthma treatments as prescribed by their doctor or nurse.[19] The top three reported reasons for not using treatments were related to cost: inability to afford treatment, treatment was too expensive, and lack of insurance coverage for the treatment.[20] Respondents with severe uncontrolled asthma were more likely to report that their asthma treatments were not covered by their insurance plan.[21] Compliance was also impacted by effectiveness (or lack

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[8] *Ibid*
[9] *Ibid*
[10] *Ibid*
[11] *Ibid*
[12] *Ibid*
[13] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 17.
[14] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 12.
[15] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 13.
[16] *Ibid*
[17] *Ibid*
[18] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 14.
[19] *Ibid*
[20] *Ibid*
[21] *Ibid*

thereof) among respondents with severe uncontrolled asthma; for other respondents, side effects of treatments were a major concern.[22]

Responses from healthcare providers echo this theme: of the 215 providers surveyed,[23] 74 percent said cost and coverage of treatment are the biggest barriers to controlling moderate-to-severe asthma in adults.[24]

Other Relevant Publications on Patient Experience: While not unpublished, AAFA would like to point towards several studies regarding the experiences of individuals with asthma. One comprehensive review of the literature found that patients with asthma prefer treatments that increase days without symptoms, but would be willing to sacrifice some treatment outcomes (specifically, symptomless days) for higher convenience and fewer side effects.[25] Additionally, research shows that there is underuse of asthma medication among racial and ethnic minorities in the United States, due in part to issues such as cost and whether or not they are insured; one study of adults aged 50-64 found that African American adults were significantly more likely to have uncontrolled asthma than Whites, and that adults in the age cohort with cost limitations were significantly more likely to have limitations of activity.[26,27]

Biologics: In our survey, few respondents overall reported significant knowledge of these new treatments.[28] Yet biologic treatment can be life changing and greatly improve quality of life for patients with asthma.[29] AAFA testimonials from several patients who have used a biologic include words like "revolutionary" and "miraculous." Quality of life has been greatly improved.[30] AAFA also supports the use of biologics because they are more targeted to different "types" of asthma than previous classes. Xolair (omalizumab), Nucala (mepolizumab), Dupixent (dupilumab), Cinqair (reslizumab), and Fasenra (benralizumab) have different indications and provide options for patients based on their specific kind of asthma. These treatments may also be an attractive alternative to frequent use of oral corticosteroids for patients with frequent exacerbations.

However, biologics are out of reach for many due to cost. AAFA receives requests every day for financial assistance because many patients fall into the gaps between insurance and patient assistance. AAFA also hears from patients expressing their frustration with the high cost of

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[22] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 14.
[23] These included physicians, physician assistants, nurses, nurse practitioners, and respiratory therapists with primary specialties in allergy/immunology, pulmonology, primary care, family medicine, and internal medicine. Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 21.
[24] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 29.

[28] Asthma and Allergy Foundation of America, "My Life With Asthma: Survey Overview (2017). 15.
[29] McCracken, Jennifer, Julia Tripple, and William J. Calhoun. "Biologic therapy in the management of asthma." *Current opinion in allergy and clinical immunology* 16, no. 4 (2016): 375.
[30] For example, patients have told us that biologics allowed them to "walk, dance, [and] sing," or be able to "visit friends with cats."

biologic treatment.[31] Despite the promise of biologics, if they are cost-prohibitive for the majority of the population, their overall impact will be minimal.

## Conclusion

Thank you for providing us with the opportunity to share our experiences as well as the experiences of those for whom we represent. We look forward to further sharing the insights of our patient community and of our scientific advisors when the Draft Evidence Report is released. Should you have any questions, please contact me at 202-974-1231 or kmendez@aafa.org.

Sincerely,

Kenneth Mendez
President and Chief Executive Officer
Asthma and Allergy Foundation of America

[31] For example, one patient wrote to AAFA "It was difficult to get my insurance to cover the Xolair. I'm concerned if I stop the Xolair but then need to restart it that my insurance will give me problems again. I have not been well enough to get my allergy shots." Another wrote, "The Xolair did not lower my eosinophils but the Nucala helped until my funding program ran out so I had to stop it."

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June 5, 2018

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review Two Liberty Square, 9th floor
Boston, MA 02109

Dear Dr. Pearson:

On behalf of the >50 Million Americans living with allergies, asthma and related conditions, we submit the following letter to the Institute for Clinical and Economic Review (ICER) and the opportunity to comment on the draft scope for ICER's review of biologic therapies for moderate-to-severe asthma.

**Burden**
Asthma, especially severe asthma, is a burden on our economy as well as patients, caregivers and healthcare providers. With >22 million Americans affected by asthma, it costs our country more than $80 billion a year. Patients with moderate-to-severe asthma account for more than 80% of the total healthcare utilization.

As you likely know:
- Asthma kills 10 people a day in the US.
- It is estimated that the number of people with asthma worldwide will grow from 300 million to more than 400 million by 2025. In America, 22 million people have asthma, roughly 1 in 12.
- 1 in 10 children in the U.S. have asthma – that's almost 6 million children – with a nearly 50% increase among African-American children.
- Among people diagnosed with asthma, 53% have a flare each year.

The burden of severe asthma restricts patients' ability to do daily activities. According to a report done by the Centers for Disease Control and Prevention (CDC), three in five people with asthma limit their daily activity due to their asthma. Each year about 15 million work days are lost due to asthma, and children miss 13.8 million school days each year due to asthma.

**It is with these patients in mind, that we provide the following recommendations to ensure a more patient-driven approach to assessing value. We have categorized our recommendations into the following core themes:**

**I. Disease Impact**
***ICER proposes to account for asthma-related impact on productivity gains & losses in a separate analysis.***
Given the burden and impact stated above, we recommend ICER consider cost-effective analyses to capture both healthcare payer and the societal perspectives. We also urge ICER to include patient community representatives as appraisal committee members with full voting rights. No one understands the burden and impact of asthma better than patients and patient advocates who have dedicated their lives to addressing this chronic condition.

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**II. Diesease Complexity**

***ICER proposes to focus this review in adults and children 6+ years of age with moderate to severe uncontrolled asthma.***

The scoping document does not address the patient population that has been defined by FDA and most clinical guideline. We believe ICER should consider the following key factors inassessing the complexity of disease: disease severity as defined by patients (impact on activities of daily living, side effects of current medications, absenteeism, presenteeism, ER visits/hospitalizations, etc.); heterogeneity & variability of disease (onset of disease, length of time since diagnosis, life expectancy, adherence & compliance differences, phenotype, etc.)

**III. Variability of Clinical Data**

***ICER proposes assessing all biologics despite product differences.***

The scoping document does not explain how ICER will account for the variability in clinical trial inclusions & exclusion criteria based on previous medication history, exacerbation history, different mechanisms of action, placebo rates, biomarkers used to identify patients, weight-based dosing differences, long-term vs short-term safety and efficacy, etc.

**IV. Health Related Quality of Life**

***ICER proposes to assess quality of life using AQLQ.***

The scoping document does not account for other validated quality of life measurements that have been utilized in the literature in severe asthma. In fact, the SGRQ is often used specifically in severe asthma due to its validity. We urge ICER to truly consider what matters most to patients and look beyond one single QOL tool to determine impact.

**Allergy & Asthma Network stands ready to partner with ICER to support the value assessment & ensure cost-effectiveness of these treatment solutions. We implore the evaluators to consider patient-reported outcomes like an increase of symptom-free days, reduction of oral corticosteroid use, reduction of ER/hosptializations and missed school/work days, rather than simply reducing asthma exacerbations or QALY's. We advocate for appropriate use of these innovative treatments and believe that when the right treatment is selected for the right patient at the right time it inevitably saves the system and individual patient.**

It is truly a promising time for those in the asthma community. Significant scientific advancements in diagnosis, phenotyping and treatment are exciting. We look forward to the opportunity to provide additional insights and/or severe asthma patient testimonies. Please do not hesitate to contact me should you have any questions.

All my best,

Tonya A. Winders
President & CEO

June 5, 2018

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

**Re: ICER evidence review of asthma treatments – draft scoping document**

Dear Dr. Pearson:

AstraZeneca appreciates the opportunity to comment on the draft scoping document for the assessment of biologic asthma treatments to ensure that patients continue to have access to innovative asthma therapies. Based on the draft scoping document, AstraZeneca respectfully submits the following suggestions for your consideration.

**Patient Population:** ***Differences in study design and execution of pivotal clinical trials for the therapies being assessed are appropriate to consider.***

As currently proposed, the population for consideration will include adults and children 6 years of age and older with moderate to severe, uncontrolled asthma and evidence of Type 2 inflammation. Assessing heterogeneous patient populations that differ from the label-indicated population for each therapy may lead to overstating or understating the cost effectiveness of treatments.

Similarly, since the objective of an economic model is to estimate effects of treatment in a population, care must be taken in extrapolating findings of studies from one cohort of patients to another patient cohort with different characteristics. Differences in patient characteristics can result from differences in trial designs (e.g., trial horizons, inclusion/exclusion criteria, and background treatments) and may manifest in differences in baseline characteristics across studies.

**Outcomes:** ***AstraZeneca appreciates the breadth of proposed outcomes outlined within the scoping document.***

Reduction in the cumulative use of oral corticosteriods (OCS) should be considered in scope as a key measure of clinical benefit. Some patients with severe, uncontrolled asthma are treated with daily OCS or frequent OCS bursts to manage their disease. Reducing daily OCS use or frequent OCS bursts can benefit patients by reducing OCS side effects and can positively impact healthcare systems by reducing OCS-related comorbidities.

**Settings:** The proposed therapies span a range of devices and formulations that have important implications for patients and healthcare providers. Differences in mode of administration, dosing frequency, and resources required for preparation and administration can be considered as part of the analytic framework.

**Patient Perspective:** ***We encourage consideration of patient preferences and potential effects on productivity in this review.***

Patient preferences can impact a value assessment directly through patient satisfaction and indirectly through potential effects on adherence. Adherence to treatment in randomized clinical

trials may not match real-world experience. Patient treatment preferences (e.g., dosing frequency, type of administration, etc.) can help inform probability of real-world adherence.

Employment-related outcomes including lost wages from absenteeism and presenteeism can be considered within scope for the value assessment.[1] According to a survey by the Asthma and Allergy Foundation of America, nearly three quarters of respondents with severe uncontrolled asthma missed at least one day of work in the past 12 months, with 41% of them reporting extended absence from work of over 10 days.[2]

AstraZeneca appreciates your consideration of the enclosed comments. As you gather evidence and further plan the analyses, we hope that our comments assist in a fair assessment for all parties, based on scientific rigor and the highest quality evidence.

Sincerely,

Frank Trudo, MD MBA

VP, Medical Affairs Respiratory

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Genentech
A Member of the Roche Group

June 5, 2018

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel:

Genentech, Inc. is deeply committed to addressing the unmet medical needs of patients with moderate to severe allergic asthma. In the U.S., Genentech, Inc. and Novartis Pharmaceuticals Corporation work together to develop and co-promote Xolair (omalizumab). Xolair is an important therapy for patients as the first and only biologic with an indication for moderate to severe persistent [allergic] asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.[1]

## Executive Summary

Genentech provides the following recommendations on the evaluation of Xolair in ICER's forthcoming review of asthma biologics:

1. Xolair should not be compared to other asthma biologics due to insufficient clinical evidence to support meaningful and valid comparisons.
   - Evidence supports the use of asthma biologics in different asthma phenotypes.
   - Inclusion criteria of clinical trials resulted in different baseline patient characteristics beyond asthma phenotype.
   - Outcome measures of pivotal studies were defined and assessed differently.
   - Change in IgE levels is an inappropriate intermediate outcome and should be excluded.
   - Prior health technology assessments (HTA) have concluded that indirect treatment comparisons between Xolair and other asthma biologics are highly uncertain or not relevant.

   Comparing Xolair to other asthma biologics within network meta-analyses (NMA) risks bias, high uncertainty, and may misinform health care decision making.

2. For patients with moderate to severe allergic uncontrolled asthma, Xolair has a unique evidence base that should be included in ICER's review of other benefits and contextual considerations. Xolair is the only asthma biologic with 15 years of post-approval experience.

### 1. Xolair should not be compared to other asthma biologics due to insufficient clinical evidence to support meaningful and valid comparisons.

#### 1a. Evidence supports the use of asthma biologics in different asthma phenotypes.

Asthma is a complex, heterogeneous disease that can be characterized by different severity levels and various phenotypes (e.g. allergic, eosinophilic, Type 2-high).[2, 3] As a result, the other current asthma biologics have a small overlapping population with Xolair in which they were studied and approved. Xolair is FDA approved for patients with moderate to severe asthma with an allergic phenotype.[1] In contrast, the anti-IL-5/IL-5 receptor agents are indicated for patients with severe asthma with an eosinophilic phenotype.[4-6] Dupilumab, which is not yet approved by the FDA, has been studied in patients with moderate to severe asthma where the expected recruitment was to have at least ~40% with blood eosinophils >300 cells/μL and did not specify an allergic status.[7] The clinical utility of phenotypic classification is still evolving.[2, 8] Asthma with an eosinophilic

phenotype has been associated with recurrent exacerbations, and blood eosinophils have been correlated with predicting response to treatment.[9-11]

**1b. Inclusion criteria of clinical trials resulted in different baseline patient characteristics beyond asthma phenotype.**
The other asthma biologic pivotal trials selected for specific biomarkers and exacerbation history, which resulted in an enriched, exacerbation prone, and more severe asthma patient population compared to the Xolair pivotal study population.[7, 12-19] Additionally, the Xolair clinical studies did not select for patients with high blood eosinophil levels through inclusion criteria or recruitment requirements. Furthermore, the lack of a run-in phase for inhaled corticosteroid (ICS) treatment optimization in comparators' trials and differences in other treatment effect modifiers (i.e. baseline exacerbation history, FEV1 and eosinophil levels) result in dissimilar populations across trials and biased comparisons.[7, 10-19]

**1c. Outcome measures of pivotal studies were defined and assessed differently.**
Asthma exacerbations were assessed at different time points and defined differently between the studies.[20] For the Xolair pivotal trials, asthma exacerbations were assessed after a 16 week ICS stable phase, and after a 12 week ICS reduction phase.[12, 13] For the other asthma biologics, asthma exacerbations were assessed at the end of the study (32-52 weeks) where the ICS dose kept constant.[7, 15-19] Asthma exacerbations were broadly defined as worsening of asthma requiring systemic corticosteroids or doubling of the ICS dose in the Xolair studies, while the other asthma biologics used a definition more similar to the American Thoracic Society guidelines published after Xolair pivotal studies were conducted.[21] Differences in definitions of exacerbations and data transformations may have a significant impact on an average estimate of exacerbations, resulting in bias and uncertainty. Other secondary outcome measures were reported and defined inconsistently (e.g. different instrument or time point) across the trials, including quality of life, asthma control, and change in $FEV_1$.[7, 12-19] These varied outcome reporting and definitions limit comparability across studies.

**1d. Change in IgE levels is an inappropriate intermediate outcome and should be excluded.**
Change in IgE should be excluded as an intermediate outcome because it is not definitively associated with clinical outcomes.[10] Allergen-specific IgE permits the characterization of atopic status. Total serum IgE has been associated with asthma; however, it is highly age-dependent and there is considerable overlap in IgE levels between atopic and nonatopic patients. Total serum IgE, allergen-specific IgE and the change in IgE are all insensitive indicators of clinical asthma outcomes and do not predict asthma exacerbations.

**1e. Prior health technology assessments (HTA) have concluded that indirect treatment comparisons between Xolair and other asthma biologics are highly uncertain or not relevant.**
Although ICER has conducted indirect treatment comparisons in drug class reviews (e.g. rheumatoid arthritis) due to significant overlap in patient populations and approved indications, we encourage ICER to consider the recommendations from several HTA agencies and a prior ICER review in asthma.[22-36] Importantly, these reviews concluded that key differences in study eligibility criteria, baseline characteristics of study populations, and outcome measurements prohibit direct or indirect comparisons.

A comparison of Xolair to other asthma biologics through network meta-analysis (NMA) is not clinically valid and is inconsistent with best practices.[37-39] Transitivity is an important assumption in NMA, which requires the population and study designs to be sufficiently similar, or at least differences that can be adjusted for by accepted methods. As outlined above, important differences in the baseline patient

populations across trials are treatment effect modifiers. There is limited evidence to allow for adjustment to minimize these imbalances. The differences in key outcome definitions and measurements also limit valid comparisons of Xolair to other asthma biologics by means of an NMA.

**2. For patients with moderate to severe allergic uncontrolled asthma, Xolair has a unique evidence base that should be included in ICER's review of other benefits and contextual considerations.**

Table 1 provides initial evidence to support ICER's request of other benefits and contextual considerations for Xolair. Since its initial FDA approval in 2003, multiple clinical trials, long-term safety studies, real-world studies and registries of Xolair have characterized outcomes important to patients with moderate to severe uncontrolled allergic asthma.

**Table 1: Evidence Supporting Other Benefits and Contextual Considerations for Xolair**

| ICER Benefits/Considerations | Xolair Supporting Evidence |
|---|---|
| Reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories | Xolair is the only asthma biologic indicated for patients 6 years of age and older.[1]<br><br>Xolair has been specifically studied in inner-city, low-income pediatric and young adults with persistent allergic asthma; Xolair was shown to reduce asthma symptoms and exacerbations.[40, 41] |
| Compared to 'the comparator,' there is significant uncertainty about the long-term risk of serious side effects of this intervention | Xolair has robust safety data from long term post marketing experience and studies, since its initial FDA approval in 2003.[1, 42]<br><br>Safety outcomes were also assessed in special patient populations (i.e. pregnant women).[43, 44] Pregnancy outcomes observed in this registry are consistent with rates published from other studies of a similar population. |
| Compared to 'the comparator,' there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention | In a 5-year observational cohort study, Xolair demonstrated improvement in asthma control from baseline to Month 6 that was maintained through Year 5.[42] |
| This intervention will have a significant impact on improving return to work and/or overall productivity | Patients newly started on Xolair experienced an immediate decrease in work impairment immediately after Xolair initiation before leveling off at month 6.[42] A similar pattern was seen for the percentage of school and regular daily activities impairment. |

Asthma is a chronic and heterogeneous condition that requires a personalized approach to treatment. It is important to preserve access to multiple therapeutic options for patients who have different needs in managing their asthma. We welcome the opportunity to further discuss the considerations set forth to inform this review.

Sincerely,

Jan Hansen, PhD
Vice President, Evidence for Access
U.S. Medical Affairs, Genentech, Inc.

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1 DNA Way, South San Francisco, CA 94080-4990

Genentech
A Member of the Roche Group

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**Re: GSK Comments to ICER's Draft Scope for the Review of Biologic Therapies for Moderate-to-Severe Asthma**

Dear Dr. Pearson:

On behalf of GlaxoSmithKline (GSK), I appreciate the opportunity to comment on the draft scope for ICER's review of biologic therapies for moderate-to-severe asthma. GSK's commitment to the respiratory community spans nearly 50-years[1] and the depth of our knowledge as a key respiratory expert is exemplified in the clinical development program for Nucala®. This program sought to address the unmet needs of patients with severe asthma with an eosinophilic phenotype who continue to experience exacerbations and/or require oral maintenance corticosteroid (OCS), despite maximal ICS-based standard therapy. Evidence of the benefits related to Nucala® include:

| Benefits | Evidence |
|---|---|
| **Richness of clinical data demonstrating predictable, robust and proven response** | DREAM,[2] MENSA,[3] SIRIUS,[4] **MUSCA**[5,†], **OSMO**[6,†] |
| **Positive quality of life (QoL) data demonstrating statistically significant and clinically meaningful improvements** | MENSA[3]; SIRIUS[4]; **MUSCA**[5,†] |
| **Long-term safety and efficacy experience (e.g., integrated safety, immunogenicity) as compared to other IL-5s** | **COSMOS**,[7,†] **COLUMBA**,[8,†] integrated safety (DREAM, MENSA, SIRIUS),[9] and immunogenicity (DREAM, MENSA, SIRIUS, **COSMOS**[†])[2-4,7,10,11] |
| **Extensive expertise and understanding of relevant sub-groups to help predict response** | Clinical utility of blood eosinophil levels of 150 cells/µL and above as a biomarker of response and analyses by baseline demographics;[2-4,9,12†-14] |
| **Depth of experience in treating patients with severe asthma** | Approximately 24,000 patients exposed[15†] and a Phase IV study assessing the use of Nucala in usual clinical practice settings of care[6†] |
| **Dedication to understanding differences between treatment options via meta-analyses, registries and indirect treatment comparisons (ITC)** | Asthma-related hospitalizations[16†] and ITCs comparing Nucala® with omalizumab, reslizumab, and benralizumab[17†,18†,19†,20†] |

† Studies and evidence that were not included in ICER's original review of Nucala.

It is with patients and their caregivers in mind, that we provide the following recommendations to ensure a more informative, relevant, and patient-centric value assessment of biologic therapies for moderate-to-severe asthma. We have categorized our recommendations into core themes: *1) Perspectives; 2) Disease Complexity; 3) Real World Evidence; 4) Quality of Life; and 5) Variability- Systematic & Other;* each are discussed in detail below.

**1. Perspectives**

*ICER proposes to account for asthma-related productivity gains and losses in a separate analysis (p.6).*

**Response:** It is estimated that asthma leads to an annual cost of $56 billion, including $50.1 billion in direct costs and $5.9 billion in indirect costs to society.[21] Severe asthma patients and their caregivers experience significant impact on productivity, work, and relationships.[22] Coupled with the body of evidence that has shown the correlation of asthma severity to direct and indirect costs,[23,24,25,26] there is strong rationale to adopt a societal perspective as the base case for this value assessment.

**Recommendations:** We recommend that ICER adopt the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine, which calls for all cost-effective analyses to capture both healthcare payer and the societal perspectives.[27] *Secondly, we urge ICER to include patient community representatives as standing appraisal committee members, with full voting entitlements.*

**2. Disease Complexity**

*ICER's target patient population for this review is adults and children ages 6 years+ with moderate to severe, uncontrolled asthma.*

**Response:** The draft scope inadequately addresses the targeted patient population of patients with severe asthma with an eosinophilic phenotype, which is clearly defined by an FDA-approved indication, and is further supported by irrefutable evidence to predict exacerbations in this disease state. Specific factors that ICER should consider are:

- **Disease severity —** the frequency and risk of asthma exacerbations is shown to increase with indicators of disease severity. Further, physicians, guidelines, and the FDA distinguish severe asthma as a separate disease state from moderate asthma, thus moderate and severe asthma populations warrant separate evaluations.
- **Severe asthma with an eosinophilic phenotype —** this FDA-recognized asthma subpopulation must be taken into consideration in all analyses and models as it is supported by multiple GSK- and competitor-led clinical trials.
- **Clinical trial heterogeneity —** the heterogeneity between clinical trial populations within pivotal trials for the included comparators (e.g., eosinophil level, OCS use, background therapy, ACQ score, exacerbation history, and patient demographics) require adjustments when assessing clinical efficacy and cost-effectiveness (see Table 1).

**Recommendations:** ICER should transparently differentiate moderate asthma from severe asthma. We also recommend that ICER consider appropriate subgroups for analysis, prioritizing the aforementioned factors (eosinophilic phenotype, exacerbation history, clinical trial population heterogeneity) and assess the feasibility of a propensity-matched approach or alternative contingencies, to adjust for between-trial differences.

**3. Real World US Evidence**

ICER has a responsibility to improve the evidence synthesis and modeling approach from the previous assessment of Nucala® (mepolizumab), to ensure a more transparent and objective value assessment of included therapies. We believe that the following recommendations will improve the relevance of this review for US payers and policy stakeholders.

**Recommendations:**

- ICER must ensure that modeling assumptions appropriately account for drug-specific dosing considerations, including but not limited to, weight-based dosing and loading dose requirements. *Failure to accurately capture the compounding economic impact of early discontinuation for any product requiring a loading dose will result in overestimation of value and misleading conclusions; furthermore, the economic impact of a patient cycling on and off treatment when a loading dose is required is unknown*.
- ICER should employ accurate assumptions for adherence/compliance based on real world evidence of patients with moderate asthma and severe asthma. *It is inappropriate to gauge the value of an intervention without adequately adjusting these assumptions based on evidence from peer-reviewed literature.*[28]
- ICER should adopt shorter time horizons to closely mirror real-world use (e.g., 1-year, 5-year, 10-year), especially if biosimilars are contemplated within these time horizons. *Central to this will be ensuring alignment on real-world patient compliance/adherence assumptions for biologics and dosing considerations for products in this review.*
- ICER should adopt a comprehensive budget impact analysis (BIA) approach, which includes all comparators, not simply the newest therapy and realistic adoption rates that accurately reflect the anticipated uptake of therapies based upon real world utilization. *Failure to account for these assumptions will limit the utility of the review to meaningfully inform payers, as the BIA will not be aligned to real world formulary decision-making.*

**4. Health-Related Quality of Life**

*ICER proposes to review and assess symptom scale/quality of life using AQLQ (p.4).*

**Response:** The scoping document does not include the robust HRQoL data, as measured by SGRQ in the mepolizumab clinical trial program: MENSA,[3] SIRIUS,[4] and MUSCA.[5] The SGRQ was selected because of greater face validity regarding aspects of asthma important to patients with severe asthma and frequent exacerbations, as compared with the AQLQ. Additionally, a body of evidence supports the SGRQ as having construct validity and responsiveness specifically in patients with severe asthma.[29,30,31]

**Recommendation:** ICER must include evidence of HRQoL impacts, as assessed by SGRQ.

**5. Variability (Systematic and Other)**

The scoping document does not address how ICER will account for product specific differences that may challenge the estimation of comparative clinical effectiveness (see Table 1). We request that ICER formally consider the following factors in its clinical and economic review:

- **Variability in the enrollment criteria regarding background inhaler therapy —** Nucala® was studied in patients optimized on inhaler therapy (representing the patient group with highest unmet need), while other development programs were not as targeted to this population. ICER must account for differences in inhaler therapy across trials.
- **Variability in disease severity/exacerbation history** (e.g., inclusion/ exclusion criteria, definitions of exacerbation) **—** will require adjustment when assessing clinical effectiveness. For example, patients enrolled in Nucala® clinical trials had severe asthma with an average of 3.6 exacerbations prior to treatment,[2,3] as compared with patients enrolled in trials for resilzumab[32] and dupxient[33], with an average of 2 or 3 exacerbations at baseline. Given these types of differences, comparisons using percent exacerbation reduction across included biologics are inappropriate and may bias the results of the review.
- **Variability in placebo rates across pivotal trials of included biologics —** Differences in reported placebo rates across biologics, (i.e., mepolizumab, DREAM and MENSA were 2.4 and 1.74;[2,3] the reslizumab phase 3 study was 1.6;[32] benralizumab's two phase 3 studies were 1.3 and 0.93;[34,35] and a phase 3 dupilumab study was 0.97.[36]) highlight the challenges and adjustments required in analyzing the comparative clinical effectiveness in this review. In the absence of patient level data to facilitate adjusted indirect comparisons, ICER should consider more traditional indirect comparison approaches such as the Bucher method.[37]
- **Biomarkers are critical to identify clinically appropriate patients and set expectations for treatment response among patients, providers, and payers**. Nucala® is a targeted therapy with a biomarker that demonstrates a clear dose response based on eosinophil level, ensuring that only appropriate patients receive Nucala®. Reduction in exacerbations for patients receiving Nucala® increases with eosinophil levels (≥150 cells/µL is 52%, at ≥300 cells/µL is 59%, at ≥400 cells/µL is 66% and at ≥500 cells/µL is 70%).[38] In contrast, a pooled analysis of benralizumab's pivotal studies found lower rates of reduction in exacerbations at similar eosinophil levels for Q8W dosing (≥150 cells/µL is 37%, at ≥300 cells/µL is 43%, at ≥450 cells/µL is 50%).[39]
- **Inconsistent clinical trial results between studies for newer therapies —** Differences in the percent reduction in exacerbations from benralizumab's two phase three studies for patient with ≥300 cells/µL on Q8W were: 51%[34] and 28%[35]. In contrast, Nucala® has demonstrated consistent exacerbation reduction across multiple clinical studies (i.e., MENSA and MUSCA were 53%[3], and 58%[5]). Even when the analyses were limited to those who received the most intensive care at the ER or hospital, a meta-analysis of studies (of at least 24 weeks' duration) found that exacerbations that required hospitalization and/or ER or hospitalization alone were both significantly reduced by 51% in subjects who received mepolizumab compared with those who received placebo ($P = 0.004$ and $P < 0.001$, respectively).[16]
- **Lack of long-term efficacy and safety data for newer products —** In contrast, more than 24,000 patients have received Nucala® during its 2+ years of clinical use in the US.[15] COLUMBA, the first study in the IL-5 class to follow patients long term (up to 4.5 years), demonstrated the sustained efficacy and safety of Nucala®.[8]
- **Limited understanding on the impact of differentiated mechanisms of action (MOA) among products —** MOAs may impact both drug efficacy and side effects. To date there is limited evidence and knowledge of the clinical consequences of near complete eosinophil depletion (as observed with benralizumab) vs eosinophil reduction (Nucala®, reslizumab, dupilumab).[40] Even slight nuances among the IL-5 inhibitors versus IL-5 receptor alpha-directed cytolytic monoclonal antibody should be considered, as these may contribute to known differences in outcomes.[41]

These comments are not exhaustive and we look forward to exploring these and other related issues with you throughout this review.

Sincerely,

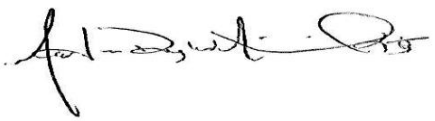

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Table 1. Heterogeneity of Populations Across Clinical Trials Focused on Exacerbation Outcome Measures with Biologics for the Treatment of Asthma

| Description | Omalizumab | | Mepolizumab | | Reslizumab | | Benralizumab | | Dupilumab |
|---|---|---|---|---|---|---|---|---|---|
| FDA-Approved Indication for Asthma | Moderate to severe persistent asthma in 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 | | Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype | | Add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype | | Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype | | FDA review pending |
| Dosing / Route of Administration | 75-375 mg SC every 2 or 4 weeks based on serum total IgE level and body weight | | 100 mg administered SC once every 4 weeks | | 3 mg/kg once every 4 weeks by IV infusion over 20-50 minutes | | 30mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter | | Asthma dose pending |
| Exacerbation Trials | Busse 2001[42] | Soler 2001[43] | DREAM[2] (75/250/750 mg IV) | MENSA[3] (75 mg IV & 100 mg SC) | 3082[32] | 3083[32] | SIROCCO[34] | CALIMA[35] | QUEST[33] |
| SoC | 420 to 840 µg/day of BDP or equivalent ≥3 months | N/A | ≥880 µg FP equivalent/day ± maintenance OCS + controller | ≥880 µg FP equivalent/day + ≥3 months controller | ≥440 µg FP equivalent/day ± controller (including OCS) | | High dose ICS + LABA | ICS (>250 µg or ≥500 µg FP or equivalent) + LABA for ≥12 months | High dose ICS (≥500 µg FP or equivalent) + ≥3 months controller |
| Blood EOS, cells/µL | N/A | N/A | ≥300 | ≥150 at initiation or ≥300 in past 12 months | ≥400 | | Any (stratified < vs ≥300 at enrollment) | | All population; 690/1638 patients with ≥300 |
| Exacerbations (past 12 months) | N/A | N/A | ≥2 | | ≥1 | | ≥2 | | ≥1 |
| Exacerbation reduction (placebo vs. active) | Steroid-Stable Phase<br>Busse: 0.3 vs. 0.2; 33%<br>Soler: 0.4 vs. 0.1; 75%<br><br>Steroid-Reduction Phase<br>Busse: 0.4 vs. 0.2; 50%<br>Soler: 0.3 vs. 0.2; 33% | | MENSA<br>≥150: 1.65 vs. 0.78; 53%<br>≥300: 1.98 vs. 0.78; 61%<br>≥400: 2.06 vs. 0.66; 68%<br>≥500: 2.11 vs. 0.58; 73%<br><br>DREAM<br>75 mg IV: 2.40 vs. 1.24; 48%<br>250 mg IV: 2.40 vs. 1.46; 39%<br>750 mg IV: 2.40 vs. 1.15; 52%<br><br>Pooled*[38]<br>≥150: 52%<br>≥300: 59%<br>≥400: 66%<br>≥500: 70% | | Pooled[32]<br>≥400: 1.81 vs. 0.84; 54% | | SIROCCO (30 mg Q8W)<br>≥150: 1.50 vs. 0.87; 42%<br>≥300: 1.33 vs. 0.65; 51%<br><br>CALIMA (30 mg Q8W)<br>≥150: 1.10 vs. 0.70; 36%<br>≥300: 0.93 vs. 0.66; 28%<br><br>Pooled*[39] (30 mg Q8W)<br>≥0: 36%<br>≥150: 37%<br>≥300: 43%<br>≥450: 50% | | Dupilumab 200 mg<br>≥0: 0.87 vs. 0.46; 48%<br><150: 0.51 vs. 0.47; 7%<br>≥150 to <300: 0.87 vs. 0.56; 36%<br>≥300: 1.08 vs. 0.37; 66%<br><br>Dupilumab 300 mg<br>≥0: 0.97 vs. 0.52; 46%<br><150: 0.64 vs. 0.74; -15%<br>≥150 to <300: 0.84 vs. 0.47; 44%<br>≥300: 1.24 vs. 0.40; 68% |

EOS = eosinophil; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-adrenergic agonist; N/A = not applicable; OCS = oral corticosteroid; SoC = standard of care

* The pooled data for mepolizumab and benralizumab were post-hoc analyses and adjusted to account for the different study durations.

***Data provided in this Table are drawn from published studies of the respective products focused on exacerbation outcome measures. These data are for information purposes only and are not intended to imply or infer the non-inferiority or superiority of products, in terms of efficacy, or safety. This information is not intended to offer recommendations for administering products in a manner inconsistent with its approved labeling.***

June 4, 2018

***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 Scoping Document for Severe Asthma Therapies*

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft scoping document for severe asthma therapies.

**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 access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

**Draft Scoping Document Comments**

As noted in ICER's scoping document, uncontrolled asthma is a substantial problem that, according to the Centers for Disease Control and Prevention, afflicts 38.4 percent of children with asthma and 50 percent of adults with asthma.[1] It is not clear from the scoping document, however, that ICER will adequately incorporate into its analysis several key issues associated with uncontrolled asthma.

These issues include:

(1) The fundamental differences among alternative long-term asthma control medicines

(2) Both the quantifiable and unquantifiable costs that uncontrolled asthma imposes on patients

(3) The income and demographic characteristics of the disease.

[1] https://www.cdc.gov/asthma/asthma_stats/uncontrolled_asthma.htm.

IfPA requests the following as ICER evaluates biologic medicines for long-term asthma control.

***(1) Account for the different causes of asthma that these medicines are designed to address***

It is imperative to account for the clinical differences among long-term asthma medicines when ICER is preparing its draft evidence report. For example, omalizumab (Xolair) is designed to treat allergic asthma patients, while mepolizumab (Nucala) and reslizumab (Cinqair) are designed to target eosinophils, a specific white blood cell linked to severe asthma.

Patients who require a long-term asthma controller that targets eosinophils will not achieve long-term control by taking an asthma controller designed to treat allergic asthma, no matter the cost-effectiveness differences between the medicines. Similarly, patients who require long-acting beta-agonists (designed to open patients' airwaves) cannot interchange their bronchodilator medicine with a medicine that treats asthma related to allergies or inflammation caused by the immune system.

These clinical differences among medications present a real challenge for ICER's comparative evaluation. Because different long-term asthma medicines are designed to treat different types of uncontrolled asthma, comparing these drugs is imprecise and therefore problematic. The cost-effectiveness of a long-term asthma medicine that is inappropriate for a patient's specific condition is simply irrelevant when evaluating the benefits created by the medicine that does actually address the patient's asthma condition.

Instead of attempting to compare these medicines against one another, ICER may find it more effective to judge each medicine individually based on symptom relief and the reduction in both quantifiable and non-quantifiable costs of uncontrolled asthma.

***(2) Fully account for the socioeconomic costs of uncontrolled asthma***

Patients with uncontrolled asthma drive the large quantifiable and unquantifiable costs associated with asthma, including:

- 3,615 annual deaths due to asthma
- 1.7 million ER visits per year
- 14.2 million doctor's office visits per year
- 439,000 hospitalizations per year. [2]

In total, asthma imposes nearly $82 billion in quantifiable socio-economic costs annually, including the costs from lost productivity and absences from work.[3] The annual, per-person medical cost of asthma is estimated to be $3,266, including the costs for prescriptions, office visits, hospitalizations, outpatient visits and emergency department care.

Some costs that are disproportionately borne by the uncontrolled asthma population are not quantifiable. These include the inability to engage in typical daily activities, the inability to exercise, inability to sleep and diminished productivity while at work or school. Uncontrolled

[2] https://www.cdc.gov/nchs/fastats/asthma.htm, and http://www.aafa.org/page/asthma-facts.aspx.
[3] https://www.thoracic.org/about/newsroom/press-releases/journal/asthma-costs-the-us-economy-more-than-80-billion-per-year.php

asthma has also been linked to comorbidities, such as psychiatric diseases and cardiac diseases, particularly in seniors.

Since the new biologics target the uncontrolled asthma population, these drugs will be particularly effective at reducing these socioeconomic costs. It is imperative that ICER's draft evidence report accounts for these impacts. It should also reflect the reality that these costs (and the resulting benefits) will be concentrated in the subset of asthma patients who have uncontrolled asthma.

***(3) Account for income and ethnic disparities***

Important income and ethnic disparities exist with respect to treating asthma. For example, asthma prevalence and mortality are highly related to poverty. Ethnicity also plays a role. African Americans are three times more likely to be hospitalized due to asthma and three times more likely to die from asthma. African American women have the highest mortality rate due to asthma. Hispanics and Puerto Ricans are also at higher risks to environmental hazards leading to allergic or asthmatic responses.

Since these groups disproportionately suffer asthma-related consequences, they will also disproportionately benefit from medicines that more effectively control asthma symptoms. ICER should attempt to account for these income and ethnic disparities in its draft evidence report.

**Conclusion**

IfPA urges ICER to account for these considerations when compiling its draft evidence report. The report will provide an inaccurate picture of the benefits created by these new biologic medicines for the treatment of asthma if the wide differences in patients' asthma conditions, the large quantifiable and unquantifiable costs, and the income and ethnic disparities that exist are not fully incorporated into the analysis.

If IfPA 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 us at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

To Whom It May Concern:

I am submitting comments on the draft scoping document for the clinical and economic review of biologic therapies for treatment of asthma associated with type 2 inflammation on behalf of two clinicians leading the development of Kaiser Permanente's national asthma guidelines.

The proposed topic is timely and well-considered although well-designed studies (RCTs) are lacking. In brief:

- The definition of uncontrolled asthma, as a measure of $FEV_1$<80%, may be problematic as many patients with severe asthma may never be able to reach 80% and thus would never be considered "controlled"
- In addition, the use of $FEV_1$ and ACQ/ACT to determine uncontrolled asthma needs to be better defined (e.g., how many measurements per year; what percentage of measurements must be below threshold, etc.)
- The time period should also be defined for exacerbations and severe exacerbations (e.g., 2+ oral steroid courses per 12-month interval)
- Some combination of interventions, such as ICS+theophylline and ICS+LTRA, may not be appropriate to define severe asthma as, for example, LTRA can be used to treat allergic rhinitis
- Adherence should also be measured as an outcome; as well as considering adherence to prescribed controller medication regiments before a biologic is started (given the risk that non-adherence patients will be stated to have "failed" more traditional controller medications)
- Comorbidities or other conditions that mimic asthma (e.g., GERD, vocal cord dysfunction) should also be considered prior to initiation of treatment with biologics.

Please let me know if you have any questions.

Sincerely, Brittany

Brittany U. Carter, DHSc, MPH
Evidence Services Consultant

Kaiser Permanente
Care Management Institute

Ph: 503-914-7662
Email: Brittany.U.Carter@kp.org

SANOFI GENZYME REGENERON

June 5, 2018

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

Dear Dr. Pearson,

Sanofi Genzyme and Regeneron Pharmaceuticals, Inc. welcome the opportunity to provide comments to the Institute for Clinical and Economic Review (ICER) analysis of the comparative effectiveness and value of biologics used for the treatment of asthma. We strongly recommend that the following key points be considered in ICER's approach in drafting the scoping document:

1. **Asthma is a symptomatic disease and the GINA guidelines recommend ongoing evaluation of treatment benefit to inform decisions of treatment adjustment. Health Technology Assessments (HTA) and published economic models consistently apply a response definition in their respective base-case evaluations. In addition, US payers apply treatment response definitions as part of their re-authorization criteria. As such, we strongly recommend that a treatment response definition be included in the base-case of the cost-effectiveness model.**

   - ICER has conducted numerous cost-effectiveness assessments of biologic agents for symptomatic conditions in the past, particularly in the area of immunology. The concept of a response definition in the base-case of the various cost-effectiveness models was common to the ICER report in rheumatoid arthritis (base-case response: ACR 20 or better), plaque psoriasis (base-case response: PASI 75 or better), atopic dermatitis (base-case response: EASI 75 or better), as well as chronic low back and neck pain (base-case response: 30% improvement in RMDQ score or better).
   - As such, a large number of published economic models assessing biologic treatments for asthma have explicitly modeled response to treatment.[1-6] For a symptomatic condition such as asthma, a lack of improvement in asthma symptoms, exacerbations, or other factors that define response may result in treatment discontinuation, be it specifically due to payer requirements, or due to physician or patient choice.
   - The criteria of response to treatment in asthma may consist of symptoms, exacerbations, side effects, patient satisfaction and lung function, as a decision-point for treatment adjustment. Control-based management is recommended by GINA, as a way to improve asthma outcomes, through a cyclical process of reviewing response to treatments, assessment and treatment adjustment.[7]
   - In the US, several large payers require evidence of treatment response for treatment re-authorization in their coverage policies of biologic agents. Commonly used response definitions include improvement in lung function, decreased frequency of exacerbations, reduction in use of rescue medications, and reduction in asthma-related symptoms.[8,9]

- Outside of the US, HTA evaluations have consistently used a response definition in their base-case cost analyses. For example, NICE has explicitly included treatment response using criteria such as exacerbation reduction,[10] asthma control,[11] and improvement based on physician's global evaluation of treatment effectiveness[12] for mepolizumab, reslizumab, and omalizumab, respectively.
- In summary, while the requirements for response definitions for treatment re-authorization vary from payer to payer, it is evident that some type of response definition should be used if the aim of the model is to reflect current reimbursement practices for biologics in asthma. Therefore, we strongly recommend the use of a symptom-based response definition in the base-case cost-effectiveness analysis since this approach closely aligns with clinical practice, treatment guidelines, as well as treatment continuation rules implemented by US payers.

2. **Patients with uncontrolled persistent asthma have substantially reduced lung function. We recommend that ICER consider the long-term impact of lung function on exacerbation risk, quality of life, and mortality in its assessment.**

- Impairment of $FEV_1$ is an independent risk factor for future acute exacerbations of asthma. The association between lung function impairment and exacerbation risk is likely to be mediated through persistent inflammation and airway remodelling.[13] Improvement in $FEV_1$ using anti-inflammatory therapy, bronchodilator therapy or combination therapy has shown to decrease risk of exacerbations.[7,14,15]
- In addition to increasing asthma exacerbation risk, impairment of lung function is associated with impaired quality of life[16] and asthma patients concomitant airflow limitation have an increased risk of mortality.[17]
- Dupilumab has shown improvement in pre-bronchodilator $FEV_1$ among persistent asthma patients who are uncontrolled on medium-high dose inhaled corticosteroids and at least one other controller medication.[18,19]

3. **Although asthma exacerbations resulting in hospitalization increase the risk of mortality, substantial evidence exists on the mortality risk associated with asthma exacerbations that occur outside of the hospital. In the recent NICE assessment for mepolizumab, the 2.48% mortality risk due to exacerbations leading to hospitalization was expanded to reflect the mortality risk in other healthcare settings. We recommend the inclusion of these mortality risk data into ICER's economic model.**

- Several studies have assessed the risk of mortality after an exacerbation or hospitalization,[20-25] with three studies[23-25] being systematically used in economic evaluations for severe asthma. Although earlier models have only considered the risk of mortality following an exacerbation leading to hospitalization, there is considerable evidence to suggest that most of deaths occurring as result of an asthma exacerbation occur outside a hospital setting.
- In the US, the 1990-2001 Multiple Cause-of-Death Files reported that only 38.5% of people with asthma-related deaths had been hospital inpatients at the time of the asthma attack that caused their death,[26] with 19% of deaths occurring in the emergency room and the remainder outside the hospital/emergency room. Additionally, the National Review of

Asthma Deaths (NRAD) in the UK reported that only 10% of people with asthma-related deaths had been treated in hospital within the 28 days immediately before having the asthma attack that caused their death.[27]

- Consequently, a more recent evaluation assessing mepolizumab incorporated fatality rates associated with exacerbations leading to an emergency room visit and physician visit. The updated fatality rates associated with exacerbations are shown in Table 1. A detailed description of the revised view on asthma related mortality by the NICE appraisal[28] committee is presented in section 5.3.6 (Mortality) on pages 201 through 205 of the document.

**Table 1:** Mortality associated with severe exacerbations

| Age group (years) | Mortality office visit | Mortality ER | Mortality inpatient |
|---|---|---|---|
| <12 | 0.01% | 0.07% | 0.10% |
| 12–16 | 0.05% | 0.23% | 0.32% |
| 17–44 | 0.06% | 0.28% | 0.38% |
| >45 | 0.38% | 1.79% | 2.48% |

ER, emergency room

4. **Finally, productivity loss associated with absenteeism and presenteeism represents the broader burden of uncontrolled persistent asthma. This burden warrants the consideration of an employer perspective in the development of the base-case cost-effectiveness analysis.**

    - The mean age of patients in the pivotal trials of the biologics of interest ranged from appropriately 43 to 53 years, representing a working age group of patients. Additionally, approximately 60% of adults in the US are covered by employer-based health insurance.[29] Given that asthma impacts work-productivity,[30] we strongly recommend that the ICER cost-effectiveness model incorporate an employer perspective and not the traditional, narrower, payer perspective, which only accounts for direct costs. The employer perspective will include additional treatment benefits, such as reductions in absenteeism and presenteeism that are relevant to employers who ultimately fund health technologies through their health insurance coverage policies.

Yours Sincerely,

Vera Mastey
Executive Director
Health Economics and Outcomes Research
Regeneron

Sheila M. Thomas
Senior Director
Global Health Economics & Value Assessment
Sanofi

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June 5th, 2018

Steven D. Pearson, MD, MSc, FRCP

President

Institute for Clinical and Economic Review

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

Dear Dr. Pearson,

Thank you for the opportunity to review and comment on the draft scoping document on Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation. We have provided comments and input for ICER's consideration in the following sections: Population and Outcomes.

**Population**

1. Three of the four approved biologic interventions being assessed are indicated for patients with severe asthma. Some of the comparators are indicated for moderate asthmatics, but reslizumab's indication doesn't include this subpopulation. Can ICER further clarify why moderate asthma is also initially mentioned in the scope of the assessment? Furthermore, Teva suggests conducting analyses on moderate asthmatics as a subgroup analysis.

2. The document specifies the use of ERS/ATS definition for severe asthma. These guidelines base the definition of severity on treatment with high dose inhaled corticosteroids (ICS) plus a second controller. This differs slightly from the GINA definition of severe asthma (requires Step 4 or 5 treatment, which includes medium dose ICS plus another controller). Given the indication for reslizumab, and the pivotal study population including patients on medium dose ICS plus another controller, can ICER clarify whether the definition also includes treatment with medium dose ICS?

3. There are patient subgroups that are traditionally considered difficult to treat, but have shown clinically significant efficacy with reslizumab, comparable to the efficacy demonstrated in the overall study population. Can ICER consider subgroup analysis of these difficult to treat types of asthma, including patients with baseline high body weight, patients with late onset asthma,

patients with refractory asthma, patients with certain comorbidities (i.e. nasal polyps), patients with higher historical healthcare resource use (exacerbations/ER visits/hospitalizations), higher baseline EOS levels, and elderly patients?

4. Reslizumab as shown high rates of response as early as 4 weeks based on FEV1 and ACQ in a large proportion of patients (Virchow JC et al., 2017; Bateman ED et al., 2016). Teva recommends that ICER consider patients who show early clinical response in the proposed assessment.

**Outcomes**

1. Will comparative efficacy include reductions in sputum EOS levels as a surrogate for treatment efficacy? The effect of reslizumab IV (3 mg/Kg) in comparison with placebo on sputum eosinophils has been evaluated in a phase II B study (Castro, et al., 2011). Patients in the reslizumab IV group showed significantly greater reductions from baseline in eosinophils in the induced sputum than those in the placebo group. By the end of therapy (week 15), the median percentage reduction in the percentage of eosinophils in the induced sputum was 95.4% in the Reslizumab IV group and 38.7% in the placebo group (P = 0.0068). This reduction in sputum eosinophils was associated with a 240mL treatment difference for prebronchodilator FEV1 for reslizumab versus placebo (p=0.0023) and the mean change from baseline to end of therapy in ACQ score was a -0.7 improvement in the reslizumab group compared to -0.3 in the placebo group (p=0.0541).

In a recent publication, Mukherjee et al (Mukherjee, et al., 2018) have compared the effect of reslizumab IV (3 mg/Kg) in 10 prednisone-dependent patients who did not achieve optimal treatment effect with mepolizumab 100 mg SC. In this study, reslizumab IV reduced sputum eosinophils by 91.2% (P = 0.002). The authors commented: ‘’the decrease in percent sputum eosinophil was greater with reslizumab (by 42.7%) compared with mepolizumab (by 5.0%) and this was associated with greater improvement in ACQ (P = 0.01; ANCOVA between before and after treatment, mepolizumab vs. reslizumab, adjusted for baseline prednisone)’’.

2. The scope document describes severe asthma as a “waxing and waning” disease. The impact on quality of life and symptom control of severe asthma and its treatments has been well documented (Reddel, et al, 2009) and has been measured with various validated scales including the AQLQ (Juniper, et al., 1999), ASUI (Bime, et al., 2012), and ACQ (Suillivan, Ghushchyan, Campbell, et al., 2017). Persistent treatment benefits, beyond exacerbation control, should be accounted for in the health economic model as patients may have morbidity separate from their exacerbations. Can ICER expand on how benefits beyond exacerbation control will be incorporated in each health state to account for the full spectrum of quality of life benefits? Can

ICER provide further detail on the “asthma non-exacerbation” health state included in the Markov model (i.e. what is included in the definition of “day-to-day asthma symptoms”)?

3. In addition, reslizumab has also shown long term sustained safety and efficacy in a cohort followed up to 2 years (Murphy, K, et al, 2017). Teva recommends that ICER also take in consideration the value of sustained clinical response to treatment, since severe asthma is a chronic condition.

Once again, thank you for the opportunity to review this scoping document we look forward to having further discussions on the comments, including providing further clarity if needed.

Sincerely,

Rinat Ariely, PhD
Senior Director, Global HEOR
Global Health Economics and Outcomes Research
Global Medical Affairs
TEVA Pharmaceuticals

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