October 22nd, 2018

Ellie Adair MPA
Program Manager
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

Dear Ms. Adair,

AstraZeneca appreciates the opportunity to respond to the draft report released on September 24th, 2018. Herein, we provide you with comments to further inform the evaluation of Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation being conducted by the Institute for Clinical and Economic Review (ICER). Our comments are organized into categories, generally aligned with the order of presentation in the draft report:

- Consideration for Patients
- Price Input
- Modeling Framework

Consideration for Patients

Severe asthma is a heterogeneous, complex disease with high unmet need requiring novel therapies.[1-3] Value assessments of novel therapies using aggregate clinical trial data do not fully apply to individual patients with severe asthma and may impact choice and limit shared decision-making between patients and providers. The framework utilized in this report inadequately captures value from individual treatment responses, patient and healthcare provider preferences, and overall treatment satisfaction. Biologic treatment options for severe asthma should align with healthcare provider and patient priorities determined through shared decision-making to optimally deliver precision medicine and reduce the burden of the disease.

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 the probability of real world adherence.

The economic model differs from real-world experience in several ways that are relevant to multiple stakeholders. The assumption in the model of perfect adherence is not likely to reflect real-world usage and does not account for discontinuations based on clinical and other factors determined by the shared decision-making process between patients and providers. Although the model accounts for the value of patient time associated with exacerbations, it does not account for value of patient time related to mode or frequency of treatment administration.

Price Inputs

AstraZeneca agrees with the importance of providing accurate price comparisons within the modeling framework. Our concern is that the preliminary results utilize different reference prices for these biologics, limiting understandability and pragmatic application to most payers. We, therefore, recommend the use of Wholesale Acquisition Cost (WAC) pricing consistently for all treatments in the model. WAC is the most transparent and verifiable

reference price. We believe that WAC rather than Federal Supply Schedule (FSS) pricing should be used because FSS pricing is applicable to a nominal market segment. FSS also tends to favor products that have been on the market for longer periods of time, since price increases are not captured within the FSS price calculations. Additionally, any other manufacturer provided price is subject to varying methodological assumptions, limiting price point comparability.

For transparency and relevance to the majority of stakeholders, we strongly recommend that a sensitivity analysis be conducted using WAC prices across all products if WAC prices are not universally utilized in all main/base-case analyses. Despite the loading dose in the first year, less frequent administrations during subsequent years mean that Benralizumab has a significantly lower average annual WAC cost compared to other biologics. Based on the data provided in the ICER Draft Report (Table 4.8 Treatment Costs and Details), we have calculated the following average annual WAC cost over a patient's lifetime for each treatment being studied.

Biologic	Annual Average WAC Cost
Omalizumab	$39,054
Mepolizumab	$37,247
Reslizumab	$31,644
Benralizumab	$30,955
Dupilumab	$38,037

The reported net prices for Omalizumab and Mepolizumab are derived from individual, manufacturer-specific assumptions that are inconsistent, further supporting using WAC as a consistent price comparison. If all base-case analyses do not use WAC, then we provide an imputed net price per administration of $4,265 for Benralizumab, a price that includes government statutory rebates, allowances, and returns. This translates to an average annual net cost of $27,779 over a patient's lifetime. We recommend that this price be used in any base-case analyses that do not utilize WAC.

Modeling Framework

Oral corticosteroid (OCS) Sparing

The benefits of OCS sparing due to treatment with biologics are not clearly captured in the economic model. Evidence indicates that cumulative OCS exposure in patients with asthma is associated with a quantifiable increased risk of OCS-related adverse events and should be accounted for in the model.[4,5] In addition, the model framework description does not provide adequate details on how the clinical benefits of OCS reduction in patient treated with biologics are captured.

In the ZONDA trial, patients enrolled on daily maintenance OCS and who received Benralizumab realized greater exacerbation risk reductions compared to placebo in the setting of OCS withdrawal.[6] We recommend the analyses use respective exacerbation rate reductions demonstrated in the placebo-controlled biologic OCS sparing trials for patients on chronic OCS.

We do not agree with including efficacy data on OCS-sparing from non-placebo controlled, open-label trials. Placebo-controlled, protocolized OCS sparing trials have been designed to determine the lowest effective OCS dose required to maintain asthma control prior to study randomization and initiation of OCS reduction. Additionally, single arm, open-label designs

are less robust at determining treatment effects, particularly since controlled trials have demonstrated up to a median 50% reduction in OCS from baseline in the placebo arms, highlighting the difficulty in demonstrating an effect above placebo.[7]

Clinical Comparative Effectiveness

AstraZeneca presented data at the 2018 European Respiratory Society meeting on a 56-week safety extension trial (the BORA study) for patients completing the pivotal, phase 3 SIROCCO and CALIMA asthma exacerbation studies.[8] The data from the BORA study demonstrate that the observed adverse event profile with Benralizumab is similar in year 2 of therapy to that of year 1 and that clinical benefits are maintained. These data are included in this response.

We note that ICER grades evidence from each manufacturer using qualitative and quantitative criteria. On page 31 of the draft ICER report, the Benralizumab studies are qualitatively described as 'relatively small studies of short duration'. We request that this statement be amended to accurately reflect that the durations of the Benralizumab phase 3 asthma exacerbation trials were either comparable to or longer than other studies included in the review. The pivotal asthma exacerbation studies, SIROCCO and CALIMA, had durations of 48 and 56 weeks, sufficiently long enough to account for the influence of seasonal factors on exacerbation rates.[9,10] Studies described in this report with shorter treatment periods may not adequately capture such factors.

In section 3, the report describes exacerbation reductions in clinical trials as not differentiated: "none of the drugs are significantly better than the other active therapies." We therefore disagree with the inclusion of Appendix B as it does not provide adequate context regarding the limitations of indirect treatment comparisons. Conclusions from these analyses may be misconstrued as scientifically robust, direct head-to-head clinical trial comparisons. The methodological limitations not discussed in the draft ICER report must be considered in the interpretation of the results. If Appendix B is included in the final report, we request the inclusion in the appendix of the recently published matched adjusted indirect comparison (MAIC) comparing Benralizumab to Mepolizumab and Reslizumab (European Respiratory Journal).[11]

MAIC controls for the influence of treatment effect modifiers among heterogeneous populations across trials. This contrasts with a standard indirect comparison of treatment effects which do not adequately account for such differences despite stratification, and, therefore, heterogeneity between the two populations persists.

Thank you for taking our comments into consideration.

Sincerely,

Frank Trudo, MD

Vice President, US Medical Affairs, Respiratory

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Appendix: AstraZeneca comments on Institute For Clinical and Economic Review Draft Evidence Report "Biologic Therapies For The Treatment of Asthma Associated With Type 2 Inflammation: Effectiveness, Value and Value-Based Price Benchmarks"

Please note that the comments below are focused on Benralizumab; specific data regarding other non-AstraZeneca products was not fact checked. **The enclosed information should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the Prescribing Information for AstraZeneca products.**

No	Page	Line	Original Text or Section/Topic	Comments or Proposed Replacement Text (suggested edits/additions in red text)	Rationale for Change
1	18	Table 3.1, 'Standard of Care Therapy' Row, Benralizumab column	Medium to high dose ICS with LABA	Medium to high dose ICS with LABA with or without other controllers including oral corticosteroids	To be consistent with clinical publications and for accurate reflection of patient population. References 1 and 2.
2	18	Table 3.1, 'OCS Use' row, benralizumab column	+	Suggest qualifier since patients were permitted to be on OCS as an additional controller: Or a temporary increase in a stable, background dosage of oral corticosteroids.	To be consistent with clinical publications and for accurate reflection of patient population. References 1 and 2.
3	18	Table 3.2, 'ED Visit or Hospitalization' row, benralizumab column	+	Suggest qualifier: ED visit requiring systemic corticosteroids or hospitalization	To be consistent with clinical publications and for accurate reflection of patient population. References 1 and 2.
4	22	Table 3.7, 'Mean Difference In Blood eosinophil Levels Between Treatment and Placebo', Benralizumab row.	105	Suggest a callout that this is a % change from baseline for treatment	Other values provided in table for other products are not percentages, but mean numerical changes for treatment versus baseline. Reference 3.

No	Page	Line	Original Text or Section/Topic	Comments or Proposed Replacement Text (suggested edits/additions in red text)	Rationale for Change
5	46	'Scenario Analysis', paragraph 3, line 4.	….0.58 for benralizumab versus SoC;	…0.59 for Benralizumab versus SoC;	To be factually consistent with publication. Reference 3.
6	93	Row 5, Benralizumab, SIROCCO, 'ACQ score' and 'exacerbations in prior year' column	ACQ score 2.87; Exacerbations in previous year 3.1.	ACQ score 2.81 Exacerbations in previous year 2.9	It appears that values for all other parameters are the mean for the three treatment groups in the full intent-to-treat population. The suggested modification are the means for these two parameters for the full intent-to-treat population. Reference 1.
7	93	Row 5, Benralizumab, SIROCCO; 'OCS use' column	NR	16%	OCS use was reported in published supplementary appendix to study publication. (Suggested value is mean of the full intent-to-treat population). Reference 4.
8	94	Row 1, Benralizumab, CALIMA; 'OCS use' column	NR	9%	OCS use was reported in published supplementary appendix to study publication. (Suggested value is mean of the full intent-to-treat population).

No	Page	Line	Original Text or Section/Topic	Comments or Proposed Replacement Text (suggested edits/additions in red text)	Rationale for Change
					Reference 5.
9	94	Row 2, Benralizumab, ZONDA; 'OCS use column'	NR	100%	OCS use was reported in this OCS-sparing trial publication Reference 6.
10	98	Row 4. Benralizumab CALIMA; 'ACQ score' column	NR	≥1.5	ACQ inclusion criteria reported published supplementary appendix to study publication. Reference 5.
11	99	Row 1, ZONDA, 'FEV_1 criteria', 'FEV_1 reversibility', 'exacerbations', 'ICS criteria', 'OCS criteria' columns.	NR	FEV_1 Criteria = <80% predicted FEV_1 Reversibility = ≥12% and 200 mL Exacerbations = ≥1 ICS Criteria = total daily dose equivalent to ≥ 500 mcg fluticasone dry powder formulation OCS Criteria = On OCS (7.5-40 mg/d prednisone/prednisolone equivalent ≥ 6 months)	Criteria reported in published supplementary appendix to study publication. Reference 7.
12	111	Row 7, Fitzgerald 2017, CALIMA, 'Change in ACQ' column	Benralizumab 30 mg q 4 weeks = -1.4 Benralizumab 30 mg q 8 weeks = NR Placebo = -1.16	Benralizumab 30 mg q 4 weeks = -1.38 Benralizumab 30 mg q 8 weeks = -1.44 Placebo = -1.19	To be consistent with the values reported in the published results of the trial. Reference 2.

No	Page	Line	Original Text or Section/Topic	Comments or Proposed Replacement Text (suggested edits/additions in red text)	Rationale for Change
13	114	Row 9, Bleecker 2016, 'n' column	Benralizumab 30 mg q 4 weeks = 293 Benralizumab 30 mg q 8 weeks = 281 Placebo = 311	Benralizumab 30 mg q 4 weeks = 403 Benralizumab 30 mg q 8 weeks = 394 Placebo = 407	To be consistent with the values reported in the published results of the trial. Reference 1.
14	114	Row 10, Fitzgerald 2016 CALIMA, 'n' column	Benralizumab 30 mg q 4 weeks = 425 Benralizumab 30 mg q 8 weeks = 441	Benralizumab 30 mg q 4 weeks = 438 Benralizumab q 8 weeks = 428	To be consistent with the values reported in the published results of the trial. Reference 2.
15	114	Row 10, Fitzgerald 2016 CALIMA, 'injection reaction' column	Benralizumab 30 mg q 8 weeks = 3%	Benralizumab 30 mg q 8 weeks = 2%	To be consistent with the values reported in the published results of the trial. Reference 2.
16	114	Row 10, Fitzgerald 2016 CALIMA, 'headache' column	Placebo = 8%	Placebo = 7%	To be consistent with the values reported in the published results of the trial. Reference 2.

Appendix References:

1) Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting b2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127.

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Genentech
A Member of the Roche Group

October 22, 2018

Institute for Clinical and Economic Review
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Boston, MA 02109

Dear ICER Review Panel,

Genentech welcomes the discussion about the value of our medicines to patients, providers, society, and the health care system. Asthma is a heterogeneous and chronic condition which requires a personalized, patient-centric approach to treatment. In the U.S., Genentech and Novartis Pharmaceuticals Corporation work together to develop and co-promote Xolair.

The purpose of this letter is to respond to ICER's draft evidence report on asthma biologics. We are confident in the value of Xolair based on 15 years of real-world experience with more than 200,000 patients with allergic asthma.[1, 2] There were no biologics in the market when Xolair launched in 2003, and it remained the only biologic in asthma for 13 years.[2-6] During the past 15 years, Genentech and Novartis have made substantial investments in generating evidence to demonstrate the clinical, economic, and societal value of Xolair. Furthermore, this evidence advanced the science of asthma by improving our understanding of its pathophysiology and improving the clinical management of this condition.

We believe the assessment does not reflect the totality of evidence for Xolair and as a result ICER has underestimated the clinical and economic value of Xolair. We recommend the following:

1. Increase the comparative clinical evidence rating for Xolair.
2. Sufficiently and appropriately incorporate real-world evidence into the assessment of value.
3. Utilize Xolair-specific data to inform cost-effectiveness models for Xolair.

In addition, we include an Appendix to this letter with suggestions for various corrections and clarifications to the Draft Evidence Report.

1. <u>Increase the comparative clinical evidence rating for Xolair</u>.

The current evidence rating of "B" does not sufficiently account for the weight and strength of evidence for Xolair. Xolair should have a higher rating based on multiple high-quality, large randomized controlled trials (RCTs) and long-term observational studies that have been conducted to demonstrate important clinical, safety and patient relevant outcomes.[7-9] The findings from Xolair's broad evidence base consistently demonstrates reductions in symptoms and exacerbations - and their impact - in a diverse, real-world population.

Below we provide a summary of Xolair's broad evidence base by key domains of value:

Domains	Evidence
Efficacy: Xolair treatment has been associated with significant reductions in exacerbations, hospitalizations, and emergency room visits.[2, 7, 10]	A Cochrane review of 25 high quality RCTs concluded that Xolair was effective in reducing asthma exacerbations and hospitalizations.[7] Pooled analyses of Xolair studies estimate the relative risk reduction of hospitalization, emergency room visits, and unscheduled doctors' visits to be 84% per year, 61% per year, and 47% per year, respectively.[7, 10]
Safety: Xolair has the most extensive long-term safety data and experience, demonstrated in RCTs, post-marketing safety reports, and long-term real-world studies.[2, 7, 11-14]	A Cochrane review of Xolair RCTs concluded that patients treated with Xolair experienced significantly fewer serious adverse events, but more injection site reactions.[7] Real-world studies have supported the safety of Xolair treatment for up to 9 years.[2, 11-14]
Patient Experience: Xolair demonstrated positive impact on health-related quality of life (HRQoL), productivity, and activities of daily living.[15, 16]	A systematic literature review of 26 RCTs that collected patient-reported outcomes concluded that Xolair treatment improves HRQoL and asthma symptom control.[15] In a 5-year observational study, patients newly started on Xolair experienced an immediate decrease in work impairment upon Xolair initiation with the effect leveling off at month 6.[16] A similar pattern was observed for school and regular daily activities impairment.
Pediatric Population: Xolair demonstrated efficacy and safety in pediatric patients 6-17 years.[17, 18]	In RCTs, Xolair consistently demonstrated a reduction in asthma exacerbations with fewer hospitalization and days missed from school.[17, 18] Real-world studies of longer duration and follow-up observed results consistent to those in the RCTs.
Specific Populations: Xolair has evidence generalizable to real-world populations with demonstrated safety and effectiveness in specific populations that are frequently excluded from clinical trials, including older patients, pregnant women and inner-city adolescents.[19-21]	Older patients: Xolair exhibited efficacy in older patients (>50 years) that was similar to that experienced by the general study population and reduced the risk of asthma exacerbations in a pooled analysis of 5 double-blind, placebo-controlled trials.[19] Pregnancy: Perinatal outcomes observed in a Xolair registry were consistent with rates published from other studies of a similar population.[20] At-risk: Xolair has been specifically studied in inner-city, low-income pediatric and young adults and was observed to reduce symptoms and exacerbations in these patients.[21]
Real-World Effectiveness: Xolair's extensive breadth of evidence extends beyond traditional clinical trials and provides insights on its effectiveness in real-world settings.[8, 9]	A meta-analysis of 25 observational studies, concluded that Xolair outcomes in the real-world are consistent with the efficacy data observed in RCTs.[8] PROSPERO, a prospective observational study of 806 U.S.-based patients, demonstrated consistent improvements in exacerbation rate, hospitalization, and asthma control following initiation of Xolair.[9]

The assessment of comparative clinical effectiveness should be updated or corrected to reflect all available evidence for Xolair.

1.1. Published data supporting the clinical benefit associated with Xolair is missing.

Recommendation: The mean difference in ACQ score for Xolair (vs placebo) should be updated from "Not Reported" to -0.41 (-0.68, -0.14) from the XPORT study (Table 3.5).[22] The XPORT study was a randomized, double-blind, placebo-controlled withdrawal study that included patients receiving long-term Xolair treatment, which may not be comparable to a study in treatment-naïve patients. However, patients continuing Xolair had a benefit in ACQ score vs placebo, and the mean (standard deviation) change in ACQ score from baseline to week 52 of 0.22 (0.66) compared with placebo 0.63 (1.13).

1.2. The effect of asthma biologics on blood eosinophil levels should be excluded from the assessment of clinical benefit.

Recommendation: Remove the section on blood eosinophil levels (page 22). Although asthma biologics have reported effects on changes in blood eosinophil levels, reduction in blood eosinophil levels have not been correlated with clinical outcomes such as asthma exacerbation. Inclusion of blood eosinophil levels as a surrogate marker of response risks misinforming health care decision making.

1.3. The long-term safety and effectiveness of Xolair is misrepresented in the evidence report.

Recommendation: There is a greater level of certainty associated with the effectiveness and long-term safety profile of Xolair. Xolair should be disassociated from the statement that there is a "Lack of evidence on the long-term safety and effectiveness of these drugs, particularly in older patients" (page 28). Data from real-world studies are summarized below (Table 2).[8] Pooled subgroup analyses from pivotal trials and real-world effectiveness data demonstrate meaningful benefit in older populations (>50 years of age).[19] No new safety signals outside of the current label have been identified based on annual safety reports submitted to regulatory bodies such as the FDA and EMA.[2] The effectiveness and safety of Xolair have been observed after 5, 7, and up to 9 years of follow-up.[12-14, 16]

1.4. Qualitative information on Xolair adverse events leading to drug discontinuation should be included.

Recommendation: Include conclusions from the Cochrane review that withdrawals were infrequent in studies using Xolair and that no differences were reported in the number of withdrawals due to adverse events between Xolair and placebo treated patients.[7] The Cochrane review pooled safety data across 25 Xolair RCTs, providing additional data to supplement ICER's meta-analysis of 7 Xolair studies.

1.5. The Xolair population included in the network-meta analysis (NMA) of patients with blood eosinophils ≥300 cells/μL is mismatched to other asthma biologics' population.

Recommendation: Xolair data from a pooled analysis of the pivotal trials (Casale, 2018) should inform the NMA (Table 3.11, Table 3.12, and Table D7).[23] The pooled analysis provides outcomes in moderate to severe allergic asthma patients treated with Xolair who have blood eosinophils ≥300 cells/μL. The

EXTRA study should be excluded because it uses a blood eosinophil cutoff of 260 cells/µL.[24] The EXACT study should be excluded because it was conducted in an asthma population with normal lung function (FEV1>80% predicted) and no exacerbation requirement for enrollment.[25] Excluding these studies from the analysis will reduce heterogeneity.

Table 1: Xolair Exacerbation Rates in Patients with Blood EOS ≥300 cells/µL[23]

	Post-Hoc Subgroup Analysis of Xolair Asthma Trials 1 and 2	
	EOS < 300 (n=559)	**EOS ≥300 (n=442)**
Rate Reduction vs placebo	45%	67%
Relative rate reduction (95% CI)	**0.55** (0.31- 0.97) p=0.038	**0.33** (0.17-0.64) p=0.001

*Exacerbations were defined as worsening of asthma requiring treatment with oral or intravenous corticosteroids and/or a doubling of the baseline ICS dose for ≥3 days; Abbreviations: EOS=Eosinophil; CI= confidence interval

2. <u>Sufficiently and appropriately incorporate real-world evidence into the assessment of value.</u>

While real-world data may now be available for some of the other asthma biologics, Xolair has 15 years of post-approval experience, long term observational studies, and claims-based analyses supporting its effectiveness and safety with 1, 5, 7, and up to 9 years of follow up with Xolair.[12-14, 16, 26, 27] An independent meta-analysis of 25 real-world observational studies of Xolair conducted between 2008 and 2015 provided strong quantitative evidence for the effectiveness of Xolair in clinical, health-related quality of life, and healthcare utilization outcomes (Table 2).[8] PROSPERO, a large pragmatic trial of Xolair with 806 patients in the U.S., demonstrated consistent improvements in exacerbation rate, hospitalization, and asthma control following initiation of Xolair.[9]

Table 2: Clinical and Patient Reported Outcomes from a Meta-Analysis of Xolair Real-World Studies[8]

Outcome	Results
Mean Reduction in the number of Exacerbations (95% CI) *	**2.64** (2.13-3.16)
Improvement in FEV_1, % predicted (95% CI) †	**10.6%** (8.1%-13.2%)
Improvement in Asthma Control Test, score (95% CI) †	**4.88** (2.44-7.32)
Improvement in total AQLQ, score (95% CI) †	**1.51** (1.12-1.90)

*Exacerbation reductions in the year after Xolair therapy compared with the year before treatment. †Results reported as improvement from baseline after 12 months of therapy. Abbreviations: FEV_1: Forced expiratory volume in one second; CI= Confidence interval; AQLQ= Asthma quality of life questionnaire

3. <u>Utilize Xolair-specific data to inform cost-effectiveness models for Xolair</u>.

It is best practice in health economic modeling to use the best available data to inform model assumptions.[28, 29] Xolair has data available from its own evidence base to directly inform the comparison of Xolair to SOC. The current cost-effectiveness models use key assumptions generalized across asthma biologics, resulting in biased results that ignore important differences between the therapies of interest and risk misinterpretation.

3.1. Exacerbation related inputs for standard of care (SOC) should be revised to reflect the SOC arms from Xolair studies.

The SOC arm for all cost-effectiveness models is based on an average of annualized exacerbation rates across all biologics (Table 4.5). These assumptions ignore important differences and heterogeneity of studied populations across the asthma biologics.[28, 29] The SOC data for Xolair was provided to ICER in prior communications.

3.2. Utility inputs for Xolair models should be based on the AQLQ.

The current model assumes the SGRQ for all biologics (Section 4.2), which is validated in moderate to severe COPD and not asthma.[30, 31] Patient-level non-exacerbation utility data derived from a placebo controlled randomized trial for Xolair based on the AQLQ to EQ-5D was provided to ICER previously.

3.3. Treatment responder evidence from Xolair studies should only be applied to the Xolair responder analysis.

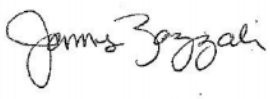
The GETE assessment has not been evaluated in other asthma biologics (Section 4.2). It has been used as a predictive tool to assess the clinical response to Xolair at 16 weeks.[32, 33] Additionally, the proportion of responders, 60.5% is based on Xolair trial data.[34]

3.4. Scenario analysis based on Xolair-specific real-world evidence should be conducted.

Conducting a scenario analysis using real-world evidence (pragmatic prospective or observational studies) complements analyses based on efficacy assumptions from explanatory trials.[35] This provides a complete picture of available evidence. A scenario analysis using data from Xolair real-world studies, such as the previously provided PROSPERO study, accounts for population heterogeneity and the clinical experience gained with Xolair since its 15 years post approval.[9]

We believe these recommendations will yield a comprehensive assessment that better reflects the value of Xolair and accounts for the evidence needs by all health care stakeholders. We welcome the opportunity to further discuss our recommendations.

Sincerely,



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APPENDIX: ADDITIONAL CORRECTIONS TO THE DRAFT EVIDENCE REPORT

	Recommendation
[Table: 2.1] Omalizumab Aetna Policy: Tier and Reauthorization Required Time (Page 11)	• Replace "Tier 4" with "Not Reported" as the tier is not specified in the clinical policy bulletins[36, 37] • Correct reauthorization required time from "3 months" to "6 months"[36, 37]
[Section 3.3] Measures of Health-Related Quality of Life and Asthma Control (Page 20, last sentence)	• Clarify whether if ICER referring to ACQ or AQLQ. Table D1 does not have AQLQ scores. • Update mean ACQ from INNOVATE from 3.9 to "Not Reported" as ACQ was not assessed in INNOVATE.[34]
[Section 3.3] Surrogate Measures of Response, Pre-Bronchodilator FEV_1 (Page 21)	• Clarify that the difference in magnitude of FEV_1 improvement observed between omalizumab and the other asthma biologics is because of differences in patient characteristics rather than the differences in asthma phenotype.[38] • Greater FEV_1 improvements have been observed in patients with % predicted FEV1 <65%, blood eosinophils ≥300 cells/μL, and airway reversibility >20%.[38]
[Section 3.3] Controversies and Uncertainties (Page 29)	• Correct the number of drugs highlighted in the review by Drs. Drazen and Harrington from "five drugs" to "four drugs."[39] • Clarify that these drugs were mepolizumab, reslizumab, benralizumab, and dupilumab. Xolair was <u>not</u> referenced or discussed in the editorial.[39]
[Section 3.4] Summary and Comment, Omalizumab and Mepolizumab (Page 29-30)	• Update the summary of dosing; pediatric, trial extension, and real-world observational studies; and cardiovascular (CV) adverse events that appear to be switched for omalizumab and mepolizumab. • Add context about CV adverse events with Xolair, highlighting how an increased risk was observed in the EXCELS study, but not in a pooled analysis of RCTs.[2]
[Section 5.2] Contextual Considerations (Page 61)	• Include long-term safety and effectiveness data from Xolair. Xolair is the only biologic with 15 years of post-marketing experience.[2] The effectiveness and safety of Xolair have been observed after 5, 7, and up to 9 years of follow-up.[12-14, 16]
[Table D1] Overview of Studies (Page 91)	• Update mean ACQ from INNOVATE (Humbert, 2005) from 3.9 to "Not Reported" as ACQ was not assessed in INNOVATE.[34]
[Table D1-D6]	• Correct section header for omalizumab studies from "Asthma with elevated IgE" to "Moderate to severe Allergic Asthma." Patients with allergic asthma can have an IgE level that is not elevated.[2]

October 22, 2018

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Dear Dr. Pearson:

On behalf of GlaxoSmithKline (GSK), I appreciate the opportunity to comment on ICER's Draft Evidence Report for Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation. GSK's commitment to the respiratory community spans nearly 50-years.[1] It is with patients and their caregivers in mind that we provide the following comments to ensure a more informative and patient-centric value assessment of biologic therapies for severe asthma. Prior to highlighting our comments, we would like to call your attention to several issues that limit the scientific rigor, accuracy, and application of findings presented in ICER's Draft Report (the details of which are summarized in this letter):

- Lack of transparency and errors in the information presented;
- Transposition of data between biologics;
- Omitted methods and analyses;
- Ambiguity in referencing (which makes verification difficult); and
- Imprecise reporting of cost-effectiveness and budget impact analyses results.

Given these limitations, we urge ICER to reassess the components of this clinical and economic review holistically and, if necessary, delay the deliberations of the Mid-West CEPAC so that the appraisal committee and external stakeholders can be informed by a more complete and accurate draft evidence report.

We have categorized our comments into six core themes: *1) Transparency Concerns; 2) Gaps in Patient and Employer Perspectives; 3) Comparative Clinical Effectiveness; 4) Comparative Cost-effectiveness Analysis; 5) Budget Impact Analysis; and 6) Draft Voting Questions.* All are discussed in detail below.

1. Transparency Concerns

GSK is committed to finding sustainable solutions to our health care challenges. We firmly believe that transparency and stakeholder engagement are critical for productive conversations about value in healthcare. **Thus, the lack of transparency in ICER's value assessment process concerns us greatly, including the lack of consistency in ICER's use of manufacturer evidence and lack of clarity on disclosure of preliminary results.** First, we are concerned about the selective and inconsistent use of manufacturer evidence. GSK provided NUCALA study data to support the exploratory NMA in the subgroup of patients with baseline blood eosinophils ≥300 cells/mcL and ≥2 exacerbations in the previous year as part of our evidence submission.[2,3,4,5] But, to our knowledge, ICER has not included these data in their NMA. Additionally, ICER has stated that data from a yet-to-be-named source will be used to conduct an exploratory network meta-analysis (NMA) for a subgroup of patients. Lack of transparency regarding the inclusion of manufacturer evidence perpetuates perceptions of subjectivity and bias in ICER's value assessment process and disincentivizes manufacturers to collaborate and engage with ICER. Secondly, ICER failed to disclose preliminary results of the review to external stakeholders, prior to the release of the Draft Report, as defined in its process. ICER has since added language in the revised guide to state that preliminary results *will not always* be disclosed. However, ICER's impromptu approach reflects a pattern of inconsistency that impedes external stakeholder engagement.

We are also concerned with the lack of transparency regarding the assumptions for the Network Meta-Analysis (NMA) and economic modeling. The gaps in the research protocol, model analysis plan, as well as the number of errors and omissions in the Draft Evidence Report prevents external validation of ICER's models and effectively impedes external stakeholders from fully understanding the outcomes of the review and the basis for ICER's policy recommendations. With ICER's goal in mind, *"to provide a fair and objective analysis of evidence as the starting point for bringing all stakeholders —patients, doctors, drug makers, insurers, and others— together to seek better*

ways to help patients gain sustainable access to high-value care", ICER research and leadership teams have an important responsibility to be more transparent, accurate, inclusive, impartial, and consistent in the value assessments undertaken.

Recommendation: We recommend that ICER provide full details of the exploratory NMA and model (e.g., an Excel file) alongside the Evidence Report to address issues of transparency and reproducibility.

2. Gaps in Patient Perspectives

Severe asthma has a significant and heterogenous impact on patients, their caregivers, and society. It is estimated that asthma leads to an annual cost of $56 billion, including $50.1 billion in direct costs and $5.9 billion for indirect costs to society, due to time off work and loss of productivity.[6] Additionally, caring for someone with severe asthma is a substantial commitment, impacting family relationships and the ability to maintain care-giver employment.[7] Coupled with the body of evidence that has demonstrated the correlation of asthma severity to direct and indirect costs,[8,9,10,11] we reiterate the need for ICER to evaluate the clinical and economic value of severe asthma medicines using a societal perspective as the base case.

It is our understanding that ICER consulted with patient groups for this value assessment, but it is unclear how ICER incorporated patient perspectives. For example, we believe that the societal perspective presented in the cost-effectiveness analysis does not fully capture, and may underestimate, the indirect burden of severe asthma. In a recent survey conducted by Asthma and Allergy Foundation of America (AAFA), approximately 72% of patients specifically with severe asthma reported missing work due to asthma symptoms, with 41% experiencing more than 10 missed work days.[7] We were very disappointed that ICER did not utilize AAFA's 2017 survey data which contextualized the burden of severe asthma based on direct patient elicitation. This was a missed opportunity in which ICER could have incorporated data directly from patients.

Recommendations:

1. We urge ICER to adopt the recommendation of the Second Panel on Cost-Effectiveness in Health and Medicine, which calls for all cost-effectiveness analyses to capture both healthcare payer and societal perspectives.[12]
2. We recommend that ICER use more recent, patient-centric estimates of lost productivity, missed work/school days due to severe asthma from AAFA[7] and fully account for the differences in indirect costs by disease severity, patient age, and care-giver impacts.
3. We recommend that ICER deepen its engagement with patient groups (such as AAFA, Allergy and Asthma Network [AAN] and others) and transparently document how patient perspectives are qualitatively and quantitatively incorporated into the value assessment process.

3. Comparative Clinical Effectiveness

a. Key Issues Related to the Misrepresentation of NUCALA Data

i. **We encourage ICER to upgrade the NUCALA (mepolizumab) evidence rating from B to B+.** NUCALA is the only IL-5 with up to 4.5 years of data showing positive clinical and humanistic outcomes. As highlighted in the Draft Report, the robust benefit of NUCALA has been confirmed through long-term, open-label studies.[13,14] Based on extensive clinical data and post-marketing safety experience, NUCALA meets the ICER criteria for a B+ evidence rating defined in the ICER report as "Incremental or Better" – moderate certainty of substantial net health benefit with high certainty of at least a small net health benefit.

ii. **ICER must correctly characterize the health-related quality of life (HRQoL) outcomes for NUCALA.** ICER incorrectly stated that none of the included agents achieved the minimum clinically important difference (MCID) for HRQoL. In three Phase 3 and 3b trials (MENSA,[4] MUSCA,[5] and SIRIUS[15]), the St. George's Respiratory Questionnaire (SGRQ) benefit from NUCALA exceeded the MCID. Inaccurately characterizing these data has major consequences at all stakeholder levels.

iii. **ICER must clarify how the AQLQ score was calculated for NUCALA**. The only clinical study for mepolizumab (DREAM) that utilized AQLQ was from the IV program, which studied a different patient population than MENSA,[4] MUSCA,[5] and SIRIUS.[15] The IV formulation was not filed for approval with the FDA. Furthermore, GSK is not aware of any bridging methodology between SGRQ (used in MENSA and MUSCA) and AQLQ. Therefore, presenting this data for NUCALA is inconsistent with the FDA-approved formulation and the populations of the confirmatory trials, and may confuse or mislead patients and providers.

iv. **ICER must clarify which studies were used to support the exacerbation Relative Rate Ratio (RRR) derivation for NUCALA**. It is unclear how ICER calculated the exacerbation RRR of 0.49 for NUCALA in Table 3.12.

v. **ICER must qualify the following statement on page 28:** *"There are several important uncertainties. First, there is a lack of evidence on the long-term safety and effectiveness of these drugs."* Therapies that are have long term data should be explicitly identified. As written, ICER appears to conflate the safety profile of included products and misrepresent the longitudinal data that has been established. NUCALA is the only IL-5 with up to 4.5 years of data showing positive clinical and humanistic outcomes.

vi. **ICER must correct dosing information presented for NUCALA to reflect the current FDA-approved label**. An incorrect dose for NUCALA is reported on page 30 ("…75 to 375 mg SC every two to four weeks…"). As stated in the prescribing information for NUCALA, the correct dose is 100 mg subcutaneously every 4 weeks.

vii. **ICER must clarify the source of a safety concern flagged for NUCALA.** ICER incorrectly implied a cardiovascular safety concern for NUCALA on page 30. The prescribing information for NUCALA does not include cardiovascular adverse events in the description of adverse events for severe asthma.[16] We believe this is a copy and paste error from the previous paragraph using data relevant to a different product.

viii. **ICER must qualify the following statement on page 31:** *"There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. The consistent benefits and minimal harms observed with the two other asthma biologics targeting the IL-5 pathway, reduces the uncertainty somewhat."* Therapies included in this review have different mechanisms of action (MOAs)/binding sites.[17] As context, ICER should specifically acknowledge that ligand versus receptor binding has been hypothesized to affect safety of therapeutic antibodies.[18] To date there is limited evidence and knowledge of the clinical consequences of near complete eosinophil depletion (as observed with benralizumab) versus eosinophil reduction (NUCALA, reslizumab, dupilumab).[19,20] While uncertainty may remain, it is well known that eosinophils play a role in maintaining health — through immune system regulation, tissue regeneration and repair, and host protection (e.g., defense against parasitic infection).[21]

b. Methodologic Concerns in the Clinical Review

ICER must appropriately account for heterogeneity in the exploratory NMA. We reiterate the inherent challenges outlined in our June 5, 2018 response letter to the ICER's Draft Scoping Document. Foremost are the challenges of heterogeneity across different clinical development programs evaluating the biologic therapies for the treatment of moderate-to-severe asthma. The letter specifically called attention to the following interrelated considerations: variability in disease severity, differences in asthma phenotypes, clinical trial heterogeneity, variability in placebo rates across pivotal trials, inconsistent clinical trial results between studies for newer therapies and the lack of long-term efficacy and safety data for newer products. As ICER plans to re-conduct an exploratory NMA with undisclosed patient-level data for the final evidence report, we resubmit our recommendations below.

Given the challenges of conducting an NMA, and in the absence of a publicly disclosed and vetted methodological approach, ICER should formally review and appraise published meta-analyses (NMAs, ITCs). ICER's critical appraisal of the multitude of methods and approaches to synthesizing trial results for the biologics in asthma would be more valuable to external stakeholders as opposed to conducting an additional analysis that may only further the confusion and misinterpretation of the value of the biologics in asthma.

Recommendations:

1. **ICER *should transparently differentiate* moderate asthma from severe asthma.**
2. **ICER *should consider additional, appropriate subgroups for analysis, —*** prioritizing key factors as described such as disease severity/exacerbation history, trial design (treatment response, and type of standard of care [SoC] therapies permitted),eosinophilic phenotype, clinical trial population heterogeneity, MOAs [see full description in our response to the Draft Scoping Document]).[3,4,5, 22,23,24,25,26] As demonstrated in Busse et al, indirect treatment comparisons with **appropriate controls for confounders and effect modifiers** such as eosinophilic phenotype can provide meaningful evidence of comparative clinical effectiveness across biologics for severe asthma.[2] In this study, which accounted for differences in Asthma Control Questionnaire (ACQ) scores and baseline blood eosinophil count, NUCALA was associated with significant improvements in exacerbation reduction and asthma control (ACQ) in specified eosinophilic subgroups, as compared with

benralizumab and reslizumab. (Note: No comparisons with reslizumab were possible below 400 cells/mcL due to the inclusion criteria of those trials.)

3. **ICER *should assess the model fit for the exploratory NMA* and *consider established guidelines*** to explore the feasibility of a propensity-weighted approach to adjust for between-trial differences.[27,28] If propensity matching fails to adequately control for confounders and effect modifiers, we recommend that ICER assess other contingencies such as outcomes regression methods.
4. **ICER *should not extrapolate long-term data to other products*.** Given the heterogeneity of the medications under assessment, particularly regarding mechanism of action, long term data from agents with such data should not be applied to those without.

c. Suggestions to Improve Face Validity and Minimize Misinterpretation of Results

i. **ICER must engage external pediatric and adult respiratory specialists with expertise in severe asthma to review the Draft Report and the presentation of evidence**. The therapies included in this review are prescribed by expert subspecialists who are qualified to differentiate between these products. External experts can advise on the **presentation of evidence** most useful to, and understandable to, clinical and non-clinical audiences.

ii. **We encourage ICER to revise the presentation of results, which currently suggests that the reviewed therapies are interchangeable.** Collectively, these therapies serve different, though partially overlapping patient populations; they have differing risks of anaphylaxis and neutralizing antibody formulation, as well as different routes of administration, dosing intervals, and administration recommendations (physician- versus self-administration). Misunderstanding the interchangeability of these agents is of great concern for providers and patients as it may lend to changes in benefit design and formulary policies that force non-medical switching for patients who actively benefit from their current therapy. GSK believes that medical provider and patient autonomy should be preserved to facilitate shared decision-making on optimal treatment options.

iii. **To reduce the likelihood of misinterpretation, ICER must appropriately represent the uncertainty in the clinical assessment and the results to reduce the likelihood of misinterpretation.** This is especially relevant, given heterogeneity of the medications under assessment (i.e., mechanism of action); as such data from agents with longitudinal data should not be generalized to agents without long-term data. Additionally, confidence intervals (CI) are a standard and expected measurement of probabilistic certainty in any statistic where the data lies in a range and are usually required in scientifically rigorous publications. When using point estimates to evaluate outcomes, we expect the use of CIs to illustrate the uncertainty of inputs where data are imprecise or longitudinal data are lacking.

4. Comparative Cost-effectiveness Analysis (CEA)

a. **ICER must transparently differentiate moderate asthma from severe asthma to accurately reflect the patient population size**. GSK recommends performing subgroup analyses of moderate asthma separately from severe asthma to more robustly and accurately represent the cost-effectiveness of each product in its indicated population. It is methodologically inappropriate to assume comparable healthcare costs for targeted biologics with different FDA-approved indications.

b. **ICER must appropriately assess and communicate the uncertainty in the economic assessment.** The sensitivity analysis results demonstrate that the model is most sensitive to utilities, namely the SoC utility value and the biologic utility value, for the non-exacerbation health state. These utility values were mapped from the SGRQ data submitted by GSK for NUCALA based on the unlikely assumption that these data will hold true for a broader, moderate asthma patient population. As suggested by the sensitivity analysis results (Figure 4.2 [page 51] compared with appendix figures E.1-E.4 [pages 121-124]), the biologic utility becomes the most sensitive parameter by a large margin for all products except for NUCALA. It is methodologically inappropriate to apply clinical data generated under specific and controlled parameters (i.e., for NUCALA in multiple clinical trials) across a much wider patient population and to the full cohort of asthma biologics, the consequences of which may mislead the broad audience this report serves to inform.

c. **ICER must use standard references across all products for the conduct of the budget impact and cost-effectiveness analyses to increase transparency and meaningfulness of results to US payers, patients, and policy-makers.** Currently, ICER has applied vastly different drug acquisition costs (e.g., from WAC to FSS to net price) to their base-case model analyses. Rough estimates of the differences between AWP to net price is approximately 30%; therefore, evaluating some products at one price point and others at a different price point

is disingenuous and may lead to inappropriate interpretations by external audiences, many who may be naïve to economic modelling methodologies.

5. Budget Impact Analysis (BIA)

a. **ICER must appropriately assess the eligible target patient population in the budget impact analyses.** ICER estimates the persistent asthma population based on asthma severity data from the Centers for Disease Control and Prevention (CDC), defined as people who are on long-term control (LTC) medications AND people with uncontrolled asthma (not well/poorly controlled) who are not on LTC medication. The population is then further funnelled to the moderate-to-severe population based on CDC long-term medication use data for asthma, defined as self-reported active asthma with ≥1 LTC medication in the past 3 months. This methodology results in an underestimated patient population for Dupixent.

b. **ICER must revisit the market uptake assumptions.** A core assumption made in the budget impact analysis is that equal market share is assumed from standard of care and biologics across the moderate-to-severe asthma spectrum. Biologics other than Dupixent and Xolair are not indicated for the moderate asthma population, therefore it is highly unlikely that any of the anti-IL5s would be displaced by Dupixent, unless these patients have progressed to the FDA-approved indication for severe eosinophilic asthma. Therefore, ICER's assumption of equal displacement from both SoC and biologic-treated populations would be incorrect. Dupixent is most likely to disproportionately displace SoC compared to other biologics in a patient population with moderate asthma. GSK recommends ICER to revisit its uptake assumptions and appropriately distribute the estimated patient population between moderate and severe asthma to produce calculations supported by scientific rigor.

c. **ICER must explicitly disclose all calculations and input sources.** Lack of transparency in CEA and BI calculations, especially considering the lack of a public source model, and imprecise reporting of inputs and results (e.g., liberal use of rounding), impedes the replication of ICER's results. Furthermore, an inability to replicate these data hinders manufacturers, especially those that support value-based pricing, from optimizing their price based on ICER's methodology prior to a public evaluation.

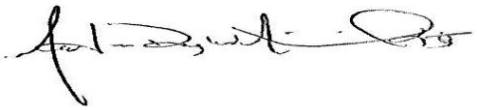
6. Draft Voting Questions

GSK is deeply concerned with the Draft Voting questions given the limited presentation of comparative effectiveness evidence, especially if the panel members' decisions are informed by ICER's exploratory NMA. For example, in draft voting question 2, ICER solicits an opinion from panel members for differences between anti IL-5 therapies. GSK would like to highlight Busse et al, 2018, which expands our understanding of comparative effectiveness evidence for the three FDA-approved anti-IL-5 therapies for severe eosinophilic asthma.[2] In this study, NUCALA was associated with significant improvements in exacerbation reduction and asthma control (Asthma Control Questionnaire) in specified eosinophilic subgroups, as compared with benralizumab and reslizumab.

Recommendation: Based on the current draft report we recommend ICER eliminate voting questions 2 through 4.

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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SANOFI GENZYME REGENERON

Sanofi Genzyme and Regeneron Comments on the ICER Draft Report on Asthma Biologics: Oct. 22, 2018

Summarized below are our main areas of concern:

- Please note that ICER's report should be updated per the approved US label for dupilumab.
- Based on indirect treatment comparisons (ITC) conducted by Sanofi Genzyme and Regeneron, dupilumab is associated with significantly lower annualized severe asthma exacerbation rates versus other biologics in comparable populations of asthma patients.
- The ICER cost-effectiveness (CE) model may not fully capture the benefits of dupilumab among patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma in terms of improvement in lung function, symptom and health-related quality of life (HRQoL) improvement among patients with type 2 comorbidities such as atopic dermatitis, and the convenience of self-administration.
- To be consistent with previously developed CE models in symptomatic diseases, we strongly recommend that ICER applies a response-definition (i.e. discontinue drug if no treatment response is observed) in their base-case analysis.

Below are additional details on our key points of concern for consideration in the ICER draft report:

A) Analysis of annualized asthma exacerbation rates via ITC

Although the draft ICER report presents numerically lower exacerbation rates for dupilumab versus other biologics in Table 3.12, Sanofi Genzyme and Regeneron have conducted an ITC which indicates that dupilumab is associated with significantly lower annualized exacerbation rates versus other biologics, including anti IL-5s and omalizumab in comparable patient populations **(Table 1).** In this analysis, a systematic and methodologically relevant approach was used for trial selection which adjusted for known treatment effect modifiers* using a pair-wise ITC; we believe this approach is more defensible than ICER's methodology.

Table 1: Pair-wise ITC of dupilumab versus other biologics on annualized severe asthma exacerbations*

Dupilumab population selected for pair-wise ITC	Trial Included	Comparison	*Exacerbation Rate Ratio (95% CI)*
Dupilumab eosinophilic sub-group: High dose ICS, EOS>=150, >=2 prior exacerbation, age >=12 (Mepolizumab-like subgroup)	QUEST 2018[1],Wenzel 2016[2]	Dupilumab 200mg/300mg vs. Placebo	0.36 [0.29, 0.44]
	DREAM[3], MENSA[4], MUSCA[5]	Mepolizumab 100 mg q4w SC/75 mg q4w IV vs. Placebo	0.50 [0.44, 0.56]
	Dupilumab 200mg/300mg vs. Mepolizumab 100 mg q4w SC/75 mg q4w IV		0.72 [0.57, 0.92]
Dupilumab eosinophilic sub-group: Medium/High dose ICS, EOS>=300, >=2 prior exacerbation, age >=12 (benralizumab-like subgroup)	QUEST 2018[1],Wenzel 2016[2]	Dupilumab 200mg/300mg vs. Placebo	0.26 [0.21, 0.33]
	CALIMA[6], SIROCCO[7]	Benralizumab q8w vs. Placebo	0.57 [0.42, 0.76]
	Dupilumab 200mg/300mg vs. Benralizumab q8w		0.46 [0.32, 0.67]
Dupilumab eosinophilic sub-group: High dose ICS, EOS>=400, >=1 prior exacerbation, age >=18 (reslizumab-like subgroup)	QUEST 2018[1],Wenzel 2016[2]	Dupilumab 200mg/300mg vs. Placebo	0.29 [0.24, 0.36]
	BREATH[8] (study 3082 and 3083)	Reslizumab 3 mg/kg q4w vs. Placebo	0.46 [0.41, 0.52]
	Dupilumab 200mg/300mg vs. Reslizumab 3 mg/kg q4w		0.62 [0.48, 0.79]
Dupilumab sub-group¶: Allergic Asthma population: (High dose ICS, Total IgE >=30 IU/mL and specific IgE to perennial aeroallergens >0.35 KU/L) (Clinically significant severe exacerbation from omalizumab trial was used in the ITC)	QUEST 2018[1],Wenzel 2016[2]	Dupilumab 200mg/300mg vs. Placebo	0.56 [0.48, 0.65]
	INNOVATE[9], EXTRA[10]	Omalizumab 150-375 mg q4w/q2w vs. Placebo	0.75 [0.64, 0.88]
	Dupilumab 200mg/300mg vs. Omalizumab 150-375 mg q4w/q2w		0.75 [0.60, 0.93]

*Known treatment effect modifiers: Baseline ICS/LABA dose, number of prior exacerbations, and baseline biomarker level from trial inclusion criteria of mepolizumab, benralizumab, reslizumab, and omalizumab were used to identify comparable sub-groups of dupilumab patients. Methodology: Bucher ITCs and random-effects model.
¶Please note that data from the ITT populations of QUEST and Wenzel 2016 (not from the US PI label population) have been used in this analysis. Therefore, the analysis may include patients who did not have an eosinophilic phenotype.

Hence, we believe the draft ICER report should be updated after including appropriate trials of all biologics and the relevant sub-group data for dupilumab in the ITC

The manufacturer of mepolizumab has presented data to regulatory authorities[11,12] confirming that 75mg IV dose is bioequivalent to 100mg SC dose. Additionally, the National Institute for Health and Care Excellence (NICE)

appraisal document also deemed these two doses as bioequivalent[13]. The mepolizumab 75 mg IV dose was studied in a 52-week trial (DREAM), which can provide a more accurate annualized exacerbation rate rather than estimates derived by annualizing the exacerbation rates from shorter duration trials of mepolizumab (example-MENSA and MUSCA). Additionally, given the well-documented seasonal variability in asthma exacerbations, effort should be made by ICER to compare longer duration trials.[14] Therefore, we again recommend inclusion of the 52-week 75 mg IV data of mepolizumab in the ITC analysis.

Although the dupilumab 24-week trial (Wenzel et al, 2016) is included in the Appendix of the ICER report, results of this trial have been disregarded within the evidence presented in Tables 3.3 through 3.10. Since this is one of the dupilumab registration trials, we strongly recommend that ICER includes this trial in the analysis. Furthermore, in the network meta-analysis (NMA) presented in Table 3.12, data from the dupilumab sub-group of patients with EOS ≥300 have been used. ICER should update its analysis by using the sub-group data of dupilumab patients with EOS ≥300 and ≥2 exacerbations, as requested by ICER, and provided by Sanofi Genzyme and Regeneron.

B) Presentation of results of intent-to-treat trial populations of biologics in the draft ICER report

The tables in the draft ICER report should be revised since side-by-side presentation of results from heterogeneous trial populations of the different biologics may lead to potential misinterpretation of results**.** ICER acknowledges the heterogeneity in trial populations of different biologics and that ITT populations should not be compared; yet, ICER continues to present outcomes data for the biologics side-by-side in Tables 3.3 through 3.10. This is highly inaccurate and compromises the credibility of the report. To rectify this, we recommend that no data are presented for non-comparable intent-to-treat (ITT) populations of the biologics within the same table. Please note that based on dupilumab's approved US label, the indicated patient populations of the different biologics are also heterogenous and should not be displayed side-by-side in the same table.

C) Clinical background and qualitative review of comparative effectiveness

Key differentiating attributes of dupilumab, including its impact on lung function, improvement in HRQoL associated with type 2 comorbidities, and patient convenience of self-administration should be acknowledged as part of ICER's clinical effectiveness assessment.

Impact of dupilumab on lung function:

Shortness of breath or difficulty in breathing is one of the most commonly reported symptoms among patients with asthma. As described in Section 1.1 of the draft ICER report, patients with uncontrolled persistent asthma have substantially reduced lung function resulting in increased risk of exacerbation, hospitalization, worsened HRQoL and increased mortality. There is substantial published evidence that impairment of FEV_1 is an important independent risk factor for future asthma exacerbations.[15-17]

Dupilumab has demonstrated rapid improvements (within 2 weeks) in lung function (pre-bronchodilator [pre-BD] FEV_1) versus placebo that were sustained up to 52 weeks of treatment; greater treatment effects were observed among patients with higher levels of type 2 inflammatory biomarkers. Furthermore, a prespecified analysis of the rate of change in the post-BD FEV_1 (FEV_1 slope after Week 4 to Week 52) showed a loss of lung function of 40 mL per year with placebo and no loss with either dupilumab dose, suggesting a potential effect of dupilumab on airway remodeling[18]. Based on the above rationale, we request that ICER acknowledges the limitations of the results based on the current CE model as it relates to the clinical benefit on lung function observed with dupilumab.

Impact of dupilumab on type 2 inflammatory diseases commonly occurring in patients with* among moderate-to-severe asthma patients with an eosinophilic phenotype or with oral corticosteroid dependent asthma*:

Type 2 inflammation is a key pathophysiologic mechanism of multiple inflammatory diseases such as atopic dermatitis (AD), allergic conjunctivitis, allergic rhinitis (AR), chronic rhinosinusitis (CRS), nasal polyposis (NP), eosinophilic esophagitis, food allergy and hives. Dupilumab has demonstrated significant late-stage efficacy in

three type 2 or allergic inflammatory diseases, indicating that IL-4 and IL-13 are required drivers of type 2 or allergic inflammation in general. Dupilumab has been shown to address this inflammation across the complete airway, which manifests in the upper respiratory tract as polyps and congestion, and in the lower airway as asthma. Development programs of dupilumab are underway for additional type 2 or allergic inflammatory diseases with high unmet need including pediatric asthma, pediatric and adolescent AD, eosinophilic esophagitis, and food and environmental allergies.[19]

Patients with moderate-to-severe asthma and having comorbid AD will benefit from dupilumab given the additional US label for moderate-to-severe uncontrolled AD. A high proportion of patients with asthma have upper airway type 2 comorbidities which worsen asthma control, increase symptom burden, and impair HRQoL. Approximately 64%-84% of patients with asthma have comorbid AR, 47.8% have comorbid sinusitis, and 19-40% have comorbid chronic rhinosinusitis with nasal polys (CRSwNP).[20-23] Consistent with epidemiology data, in the dupilumab Phase 3 trial of moderate-to-severe uncontrolled asthma[18], ~80% patients had one or more of these type 2 comorbid conditions. The most frequent comorbidity (~70% of the patients) was AR whereas CRS with or without NP was reported in ~20%, and AD in ~10% of the study population. Results of this trial indicated that dupilumab improved asthma-related outcomes and also demonstrated clinically meaningful impact on HRQoL associated with comorbid AR and CRS with or without NP.[24,25] Based on the above rationale, we request that ICER acknowledges the limitations of the current CE model as it relates to the role of dupilumab in improving HRQoL among asthma patients with type 2 comorbidities.

Patient benefit associated with the convenience of self-administration of dupilumab and related cost savings:

Asthma impacts daily living in a patient population that is largely of productive age. At the time of its marketing authorization for the treatment of moderate-to-severe asthma patients with an eosinophilic phenotype or with oral corticosteroid dependent asthma in the US, dupilumab will be the only biologic offering patients the convenience of self-administration. Considering that the cost of in-office administration of biologics can be as high as ~$1,200-$2,000 per year* and that not all subcutaneously administered biologics can be self-administered, ICER should revise Table 4.3 to clarify the benefits of dupilumab self-administration and acknowledge this as one of the differentiating attributes of dupilumab in the clinical comparative effectiveness assessment.

ICER statements in Harms section of the draft report are scientifically inappropriate. We urge ICER to revise Table 3.9 and 3.9 by limiting the content to descriptive text without commenting on statistical comparisons, numerical trends, and risk ratios.

It is misleading to compare the overall incidence rates of SAEs and AEs leading to drug discontinuation between treatment groups across trials without clarifying the specific MeDRA preferred terms, such as injection site reactions as listed in Table 3.10. Furthermore, the definition and reporting of SAEs and AEs varies across clinical trials and can also be affected by the unique patient populations enrolled with varying underlying medical conditions (e.g. OCS-dependent severe asthma vs. moderate-to-severe uncontrolled asthma patients who were not OCS-dependent) and unique circumstances (e.g. an emergent endemic infectious disease leading to hospitalization (i.e. SAE) or discontinuation of the study drug among patients from a certain region) during treatment periods. Based on the above rationale, we believe it is inappropriate to compare overall incidence rates and risk ratios for SAEs and AEs leading to treatment discontinuation between biologics. ICER's comments on harms (safety) should be based on product labels approved by the FDA since labeled safety information is based on integrated assessments of safety data from multiple clinical trials and robust assessments of causality or relatedness.

Lastly, we strongly recommend that ICER clarify the role of markers of type 2 asthma and the mechanisms of actions (MOA) of each of the 5 biologics assessed:

It is necessary to provide clarity on the roles of each of the type 2 cytokines as related to the MOA of the five assessed biologics. IL-5 is predominantly responsible for activation and recruitment of eosinophil.[26] IL-4 is crucial

*Yearly in-office administration cost: ~$1,200 - $2,000 for patients on a biweekly omalizumab treatment schedule. Payment of $49.88 payment per injection from claims analysis (CPT: 96401 or 96372) or payment based on physician fee schedule of $81.72 (CPT: 96401) as suggested by the manufacturer (https://www.genentech-access.com/hcp/brands/xolair/learn-about-our-services/reimbursement.html).

for the differentiation of naïve Th0 cells to Th2 cells, which in turn induce isotype switching to IgE production, and the production of type 2 cytokines (e.g. IL-5, IL-13) and chemokines (e.g. eotaxins-3). IL-13 also induces goblet cell hyperplasia, mucus hyper-secretion, and airway hyper-responsiveness. It is necessary to clarify that dupilumab is a monoclonal antibody to the α subunit of IL-4 receptor (IL-4Rα) shared by both the IL-4 and IL-13 receptor complexes, thereby inhibiting both the IL-4 and IL-13 signaling pathways. Dupilumab is the only biologic that targets these two key cytokines central to type 2 inflammation in asthma. Also, allergic and nonallergic asthma are highly overlapping in their clinical presentations and in the underlying inflammatory processes and biomarkers.

D) Methodology and assumptions used in the cost-effectiveness (CE) model

Asthma is a symptomatic disease and guidelines recommend the ongoing evaluation of treatment benefit to inform decisions of dose escalation, add-on therapy, and treatment discontinuation. We strongly recommend the use of a response definition as presented in the current *what if* scenario to be used as the base-case in the CE analysis since this approach closely aligns with clinical practice, treatment guidelines, previous models used in submissions to HTA bodies such as NICE, as well as management criteria implemented by US payers.

Treatment guidelines recommend the evaluation of response to treatment which may consist of symptoms, exacerbations, side-effects, patient satisfaction and lung function, as a decision-point for treatment escalation, maintenance, or dose reduction. Control-based management is recommended by the Global Initiative for Asthma (GINA) as a way to improve asthma outcomes through a cyclical process of reviewing response to treatments, assessment and treatment adjustment.[27]

- This approach implicitly assumes that, for a symptomatic condition such as asthma, a lack of improvement in asthma symptoms, exacerbations or other factors that may define response is likely to result in discontinuation of the drug, be it specifically due to payer requirements, or due to physician or patient choice.
- A large majority of previous economic models assessing asthma treatments have explicitly modeled response to treatment.[28-35] Previous economic models evaluated by NICE have consistently used definitions of treatment response to assess the CE of biologic agents for asthma. As such, we disagree with the statement made by ICER on page 43 of the draft report that there is a "lack of publicly available on treatment response definitions, proportions who respond, and the corresponding comparative outcomes for the reviewed biologics." Information on all of these parameters is available in the various publicly available NICE evaluations of asthma biologics, which are highlighted in **Table 2** below.

Table 2: Response definitions used in HTA assessments of biologics

Drug	Agency	Response definition	Time of assessment
Mepolizumab	NICE[36]	At least 50% fewer asthma exacerbations needing systemic CS in people with ≥4 exacerbations in the previous 12 months and/or A clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control	12 months
Reslizumab	NICE[37]	A clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control	52 weeks
Omalizumab	NICE[38]	Good or excellent improvement based on physician's global evaluation of treatment effectiveness (GETE)	16 weeks

- Several large payers in the US require evidence of treatment response in their coverage policies of biologics for asthma **(Table 3)** and while these requirements vary from payer to payer, they support the notion that some type of response definition should be included as the base-case in the CE model if the aim of the model is to reflect current reimbursement policies in the US.

Table 3: Examples of criteria used by major US payers in their treatment continuation/re-authorization rules for biologics

US payer/ PBM	Drug	Response definition used in continuation/ re-authorization rule	Time of assessment
Anthem UHC	Omalizumab[39,40] Benralizumab[41,42] Mepolizumab[41,42] Reslizumab[42,41]	Evidence of improvement as documented by one or more criteria: i. Decreased utilization of rescue medications ii. Decreased frequency of exacerbations iii. Increase in percent predicted FEV_1 from pretreatment baseline iv. Reduction in reported asthma-related symptoms	12 months
Cigna	Mepolizumab[43] Reslizumab[43]	History of beneficial treatment response and clinical conditions meeting all the criteria applied during treatment initiation	12 months
Express Scripts	Mepolizumab[44]	Documentation of positive clinical response as demonstrated by at least one of the following: i. Reduction in the frequency of exacerbations ii. Decreased utilization of rescue medications iii. Increase in percent predicted FEV_1 from pretreatment baseline iv. Reduction in severity or frequency of asthma-related symptoms	12 months
OptumRx	Mepolizumab[45] Benralizumab[46]	Documentation of positive clinical response to required (example: Reduction of exacerbations)	Not posted

- Finally, ICER has conducted numerous CE 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 CE 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), AD (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). We suggest that this approach be extended to model the base-case in the current asthma assessment.

An individual patient level microsimulation is more appropriate to assess a complex disease such as asthma instead of the memoryless Markov approach currently proposed

There is evidence to suggest that a dynamic relationship exists between asthma control, lung function, and exacerbation risk. However, the requirement of mutually exclusive health states as proposed in the draft ICER model does not allow patient characteristics to be retained as continuous variables with specific values over time. For example, the occurrence of a severe exacerbation would likely decrease lung function in an individual patient, which in turn would increase the risk of subsequent exacerbations in that patient. Unfortunately, the currently-proposed Markov model retains no memory of previous exacerbations or any other relevant outcomes, since it applies a constant exacerbation risk for the entire cohort and is therefore unable to track the change in risks over time. We believe a patient level microsimulation would be more accurate in assessing dynamic changes in risk and therefore more sensitive in capturing the value proposition of biologic therapy for asthma.

The net annual price of dupilumab used in the CE and budget impact model should be reduced to $31,000

In the draft evidence report Table 4.17, the annual price of dupilumab is listed at $36,000. However, in previous communications with ICER about the assessment of dupilumab for the treatment of moderate-to-severe AD, Sanofi Genzyme and Regeneron had communicated that the net annual price of dupilumab was ~$31,000. We recommend that the net annual price of $31,000 be retained for the current assessment of dupilumab in asthma. Additionally, the ICER budget impact model assumes a patient population of >6 for all biologics; however, dupilumab is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

The incremental CE results should not be displayed in a single table, but presented separately for each biologic

The current presentation of model results in Tables 4.16-17 and 4.20-24 is highly misleading. Given that the label populations of the various biologics of interest vary substantially in terms of baseline characteristics, it is inaccurate to present the numbers together within the tables. This presentation suggests that the patient populations are comparable across trials and, furthermore, that biologics with lower incremental CE are in some way superior to biologics with higher incremental CE. In fact, the incremental CE associated with dupilumab may exceed that of other biologics given that the dupilumab clinical trial program enrolled a broader set of patients with fewer baseline exacerbations and lower mean EOS levels. Hence, the incremental CE for dupilumab is inherently incomparable with the CE of the other biologics and thus requires separate reporting.

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Teva Pharmaceuticals
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October 22, 2018

Steven D. Pearson, MD, MSc, FRCP
President,
Institute for Clinical and Economic Review

RE: Draft Evidence Report for 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 evidence report for biologic therapies for treatment of asthma associated with type 2 inflammation. Our comments to ICER outlined in this letter largely focus on the evidence gaps that may be addressed by incorporating data submitted by manufacturers during the data request phase of ICER's evaluation. In this context, we respectfully submit our recommendations for ICER to consider in finalizing the analysis and report.

1. Evidence Base

- We observed in our review of the draft evidence report that ICER relied heavily on the 2014 and 2017 published Cochrane reviews, supplemented with information from available FDA product labels, for the evidence synthesis of clinical effectiveness (Farne 2017; Normansell 2014). It is unclear why the evidence solicited directly from manufacturers did not play a more substantial role in ICER's evaluation. The Farne et al (2017) Cochane review alone does not reflect the comprehensive evidence base currently available on CINQAIR®. Specifically, we note that neither the CINQAIR product label nor the Cochrane review include data for important patient subgroups for whom biologic therapy may offer the greatest value (eg, patients with GINA 4/5 and ≥2 prior exacerbations; detailed explanation provided in Section 2).
    - Evaluation of key patient subgroups is essential to reducing the heterogeneity across study populations and for assisting decision-makers in understanding where these biologic therapies may provide the most value. Accordingly, these data were submitted to ICER with this recommendation.
    - Teva, therefore, requests that ICER reconsider the current reliance on the published Cochrane reviews and place greater emphasis on the evidence submitted by manufacturers, including any relevant subgroup data, when finalizing this Evidence Report.
- In addition, ICER's application of the study inclusion criteria across comparators is unclear. ICER relied heavily on the Farne et al (2017) Cochrane review when evaluating mepolizumab, resulting in the omission of data from relevant pivotal studies (eg, Pavord 2012 and the IV 75mg arm of Ortega 2014). Moreover, the mean difference in AQLQ reported for mepolizumab vs placebo (ICER, Table 3.4) only reflects the estimates reported in Haldar et al (2009).The mepolizumab dosing utilized in Haldar et al (2009) (750 mg IV) is nearly 10 times the FDA-approved mepolizumab dose for asthma (100 mg SQ/75

mg IV bioequivalent dose) and is therefore an inaccurate estimate of the impact on quality of life associated with the approved dosing. The only AQLQ assessment we are aware of with 100 mg SQ/75mg IV of mepolizumab is in Pavord et al (2012).
    - Teva recommends increased transparency in study selection for each analysis and comprehensive inclusion of all pivotal trials utilizing marketed or IV equivalent dosing, including registration studies (75 mg IV Mepolizumab).
- ICER observed that there "remains uncertainty about the long-term durability of the benefits of [reslizumab] therapy" (ICER, page 30). However, there exists consistent, long-term data for reslizumab which represents up to four years of use including 52 weeks of studies in the pivotal trials (Castro 2015), and up to 2-3 years of follow-up in the open label extension studies (Murphy 2017; Pahus 2018) which were available to ICER but omitted from the evaluation.
    - Teva therefore requests that the evidence previously submitted by Teva to ICER for consideration be re-reviewed and incorporated in the evidence synthesis.

2. Definition of severe asthma subgroup

- As acknowledged by ICER, there is substantial heterogeneity in patient populations across comparator trials, and consequently, in product indications (ICER, page 17). It is, therefore, essential that other important parameters be included when defining the subgroup of patients with severe asthma to limit heterogeneity, improve predictability, and to ensure a relevant, robust evaluation. To better reflect actual practice considerations and to reduce variation across the patient populations, Teva previously requested in our response to the preliminary results that ICER adopt a definition which includes those patients receiving GINA Step 4 or Step 5[1] (GINA 4/5) therapy *and* who have evidence of ≥2 prior exacerbations for the base case analyses. The proposed definition is consistent with the American Thoracic Society (ATS) / European Respiratory Society (ERS) definition of severe asthma, referenced in **Table 1 (Appendix)** (Chung 2014).
    - Teva recommended that ICER conduct a subgroup analysis of the GINA 4/5 patients to identify variation in the outcomes as a result of applying an alternative definition of severe asthma and reducing heterogeneity across comparator studies.
    - Defining patients as having severe asthma by the number of prior exacerbations ≥2 was also recommended by Teva as evidence suggests that treatment effects are dependent on historical exacerbation rates. The number of prior exacerbations varied across comparator trials (by inclusion) in the ICER evaluation. Thus, use of this criterion may further reduce heterogeneity.
    - Following consultation with ICER on the preliminary results presentation, Teva proactively conducted analyses on the subset of reslizumab patients with "2 or more exacerbations in the prior year" to provide evidence that more closely aligns with comparator studies (ie, ICER, Table 3.1). These data were provided to ICER for consideration and inclusion in the draft evidence report in a timely manner, and well in advance of the report's release; however they were not included.
- Teva respectfully requests, again, that ICER includes this definition in its analyses.

[1] Global Initiative for Asthma (GINA) Step 4 (two or more controllers plus as-needed reliever medication) or Step 5 (higher level care and/or add-on treatment) therapy

- At a minimum, Teva recommends that ICER includes scenario analyses of this subpopulation of patients to allow for estimation of the full range of potential benefit and outcomes associated with all interventions.

- Teva is resubmitting these data for ICER's consideration under its academic-in-confidence policy in the **supplementary Appendix** (**Tables 1A-1F**) and requests that ICER utilizes these data when evaluating reslizumab (Wechsler 2017).

3. Patients with blood eosinophils ≥ 300 cells/µL

- ICER requested data from manufacturers in the subgroup of patients with eosinophils ≥ 300 cells/µL and ≥2 exacerbations in the year prior to randomization. The current evaluation indicates that these data were "too late for the draft review" and are therefore not included in the report. However, *all* of the reslizumab trial data were for patients with baseline eosinophils ≥ 400 cells/µL by definition as the inclusion criteria is for eosinophils ≥ 300 cells/µL.
- Teva submitted these data, plus an additional subset evaluating only the subgroup of patients with ≥2 prior exacerbations, to ICER in a timely manner and well in advance of the draft evidence report being posted. Moreover, ICER reports apparent outcomes for this subgroup analysis in the draft evidence report, and it is unclear on what evidence these analyses are based.
    - Teva therefore resubmits data on the subgroup of patients with eosinophils ≥ 300 cells/µL *and* ≥2 prior exacerbations in the **Appendix** (Brusselle 2017) and the **Supplementary Appendix (Tables 1A-1F)** as academic-in-confidence data for ICER's inclusion in the corresponding analysis.
    - Teva requests that ICER utilizes and incorporates these data when updating the NMA with additional data for the Evidence Report that will be discussed and debated at the public meeting on November 29, 2018.
- The draft report implies a threshold for response based on increasing patient blood eosinophil levels for this patient subpopulation.
    - Teva's data for patients with eosinophils ≥ 300 cells/µL demonstrate greater efficacy for patients with blood eosinophil levels >400 cells/µL (Corren 2016). These data are reported in the literature, and are also provided for consideration under ICER's academic-in-confidence policy in **Table 2A-2B** in the **Supplementary Appendix**.
    - Based on these findings, Teva strongly urges ICER to consider all evidence related to markers of disease severity instead of targeting high eosinophil levels alone, as these data are limited in predicting response to biologic therapy above an eosinophil threshold of ≥400 cells/µL. Specifically, Teva requests that ICER consider the number of prior exacerbations and background treatment when conducting analyses in order to establish a balanced baseline for comparison.
    - Published data, such as the benralizumab CALIMA study, demonstrate the increased benefit of biologic therapy in patients with greater number of prior exacerbations (Goldman 2017; Fitzgerald 2017). Teva therefore requests that ICER include a subgroup analysis of patients treated with ICS plus another controller therapy to allow for a more refined analysis of patients with severe asthma who are likely to incur higher costs of treatment.

4. Reslizumab Quality of Life Benefit

- Moderate-to-severe asthma can have a significant impact on patient quality of life and is integral to ICER's estimation of the cost per quality adjusted life year (QALY) measure of cost-effectiveness. It is therefore essential that the patient population utilized for estimating the clinical benefit also be the basis for estimating the quality of life impact. Specifically, ICER has expressed interest in evaluating the impact of therapy in the subgroup of patients with moderate-to-severe asthma **and** ≥2 prior exacerbations. Thus, Teva provides a post hoc analysis of our patient reported outcome (PRO) data in GINA 4/5 patients with ≥2 prior exacerbations (Wechsler 2017 and Table 1D).

5. Reslizumab Rate Ratios for Key Outcome Measures

- ICER notes on page 22 that, "Despite having the greatest reductions in blood eosinophils, reslizumab did not have the greatest reduction in asthma exacerbations, improvements in quality of life measure, or improvements in FEV_1." This statement is incorrect as:
    - Table 3.3 (ICER page 19) shows that reslizumab had the greatest reduction in clinical asthma exacerbations (CAEs).
    - Table 3.4 demonstrates a greater improvement in AQLQ with reslizumab compared to all drugs except mepolizumab. As mentioned in Section 1, the mean difference in AQLQ reported for mepolizumab vs placebo reflects estimates that exclude pivotal trials, and is based on dosing that is nearly 10 times the FDA approved mepolizumab dose for asthma (100 mg SQ/75 mg IV bioequivalent dose).
    - It is critical to comprehensively include all available relevant data and pivotal trials utilizing marketed or bioequivalent dosing when conducting analyses. Teva urges ICER to increase transparency in methods of study selection and inclusion of pivotal trials.

6. Consideration of Harms of Therapy When Determining Evidence Ratings

- ICER notes that "The most common side effects of reslizumab are nasopharyngitis, upper respiratory tract infections and myalgias" (ICER, page 24). It is unclear what evidence was obtained to support this as the most common (ie, ≥ 2%) side effect reported for reslizumab is oropharyngeal pain (CINQAIR [package insert]). There were no adverse drug reactions with incidence higher than 1% (CINQAIR [product monograph]). Teva requests that ICER clarify the source of this statement and update accordingly.
- In addition, ICER notes that reslizumab's potential harms include "opportunistic infections" (ICER, page 30). However, there have not been any opportunistic infections reported in any patients treated with subcutaneous or intravenous reslizumab. Teva requests that ICER remove "opportunistic infections" as a potential harm with reslizumab as this was not observed in any studies or post-marketing data related to reslizumab use as of October 16, 2018 (data on file).
- We note that there are two different anaphylaxis rates reported for omalizumab while none is listed for reslizumab (ICER, page 24). We believe that this is a typographical error and request that the sentence be corrected in accordance with the published rates reported in the corresponding package inserts.
- Although ICER notes that both omalizumab and reslizumab carry a boxed warning for anaphylaxis, it is unclear whether the boxed warning for anaphylaxis was considered as a potential harm, or what weight it was given, when determining the evidence rating for omalizumab. The harms associated with omalizumab were characterized as "small" in ICER's report without any reference to, or mention of, the

boxed warning for anaphylaxis. In contrast, ICER specifically noted the boxed warning for anaphylaxis associated with reslizumab when determining its evidence rating.

- ICER's analysis demonstrated that reslizumab has lower rates of injection site reaction compared to other biologic treatments for asthma (ICER, page 23). This is of particular note as injection site reactions were the most common adverse event for other biologic treatments for asthma. It is unclear how, or if, this benefit of reslizumab was taken into consideration when determining its evidence rating.
- Teva requests that ICER clarifies the evidence and rationale for determining the final evidence ratings, specifically as it pertains to the 2 products with black box warnings. This is essential to ensure transparency and that ratings are consistent across all interventions.

7. Impact of Treatment Response

- ICER acknowledges differences in trial designs, patient populations, and definitions of outcomes throughout the report. One important analysis that they consider evaluates the subgroup of patients who respond to therapy. In Table 4.2, for example, ICER notes that "given heterogeneity across treatment responder definitions, stakeholder comments, limited comparative outcomes evidence tied to treatment responders versus non-responders, and limited understanding of how such responder definitions would be implemented in US practice settings, the inclusion of the potential impact of treatment responders was reserved as a scenario analysis" and is ultimately carried out as a "*What-if*" analysis on the basis of insufficiently comparable evidence from omalizumab across biologic therapies.
- It may be more informative to consider a common definition of treatment response utilizing an algorithm that accounts for exacerbations and other key aspects of therapeutic benefit in determining treatment response. Utilization of such an algorithm would ensure that estimates of "one time treatment response" are derived using a robust and similar method. To the extent possible, and irrespective of any specific algorithm that ICER adopts, it is essential for the credibility of these analyses to refine the definition of treatment response in an effort to reduce heterogeneity and improve transparency.
- As discussed during a call with ICER, Teva has developed one such algorithm to predict long-term benefits of treatment for our own clinical studies. This algorithm is the topic of a recently peer reviewed manuscript (Bateman *In Press*). Teva provided this document for ICER's consideration during the data request period as academic in-confidence data under ICER's policy and offered to participate in a follow-up call to address any questions or further discuss how this may be of benefit. The algorithm has a positive predictive value of 89.9%-93.6% and a negative predictive value of 50.0%-73.3% to predict treatment response at 52 weeks of treatment.
- Rather than adopting an algorithm that aims to reduce the observed heterogeneity and reduce the likelihood of analyses that may have limited applicability or be inaccurate, ICER carried out a *"What-if"* analysis. While such analyses can be informative, Teva requests that ICER applies a universal method for identification of treatment responders to ensure a more robust and meaningful analysis of this important patient subgroup.

8. Reslizumab Net Price Data

- Applying Statutory discounts to CINQAIR utilization results in a weighted average net price of 91.5%.

9. Other Considerations in the Cost-Effectiveness Analyses

- Average patient population assumptions

- Given that each analysis is intended to be "within" trial and comparable only to SOC, it is not clear why ICER adopted a common set of model cohort characteristics (ICER, Table 4.1). This only reinforces the tendency to compare biologics to one another – particularly as it pertains to the economic analyses.

- The assumptions made and required to estimate the cost-effectiveness of therapy over a lifetime (eg, durability of effect, duration of biologic treatment, assumption that all non-responders go on SOC for the rest of their life) require over-simplification of reality and likely distort the true implications on cost of care in meaningful and decision-relevant ways. It is recommended that ICER evaluate the cost-effectiveness of therapy over shorter time horizons where assumptions may be more tenable and provide less distortion to the overall estimate of the economic impact.
- TEVA provides recent real-world evidence of OCS sparing in patients receiving CINQAIR (data on file, IMS LRx April 2015- March 2016) for ICER's consideration. Patients on chronic OCS (6 OCS claims in previous 6 months or 12 claims in previous 12 months) who received CINQAIR reduced their OCS claims by over 50% (53.8% in 6 months following start of therapy and 52.8% in 12 months following therapy). TEVA requests that ICER include these data on steroid sparing effects for CINQAIR in its cost-effectiveness analysis.
- Further, ICER's study selection choices for inclusion in the NMA are unclear. Studies included by ICER vary greatly in study phase, definition of asthma severity, standard of care response rates, study follow-up lengths, and time horizon for reporting of exacerbation rates. All of these variations can act as potential source of bias in ICER's analyses. Teva recommends ICER increase transparency in its NMA study selection and also consider other recommendations for subgroup analyses to reduce possible biases.
- As mentioned in Section 7, a "*What if"* treatment responder scenario analysis was conducted on the basis of insufficiently comparable evidence from omalizumab across biologic therapies. The methods ICER used in deriving assumptions to evaluate response after 16 weeks of treatment are unclear, along with the assumption that 60.5% of biologic-treated patients respond. Teva requests increased transparency in the methods for applying assumptions.

We respectfully request that ICER consider the above suggestions in finalizing the analyses and developing the evidence report.

Sincerely,

Rinat Ariely, PhD

Sr. Director, Global Health Economics and Outcomes Research
on behalf of Teva Pharmaceuticals

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Appendix

Reslizumab (CINQAIR) references (publicly available)

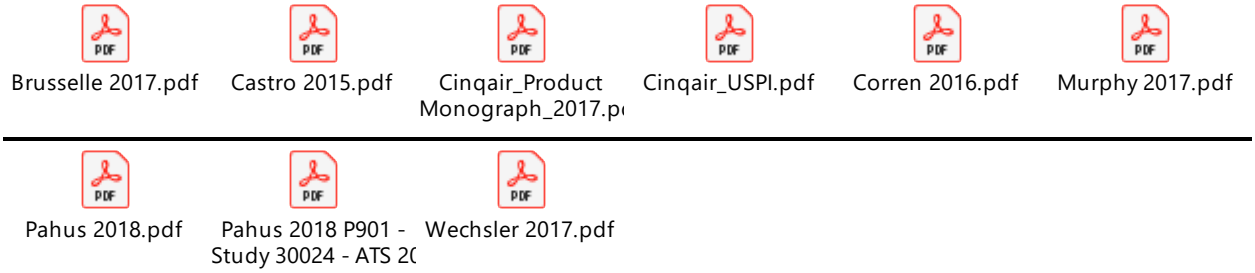

Table 1. Definition of Severe Asthma for Patients Aged ≥6 Years (Chung 2014)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS# and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy Uncontrolled asthma defined as at least one of the following:
1. Poor symptom control: ACQ consistently 1.5, ACT ,20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)
2. Frequent severe exacerbations: two or more bursts of systemic CS (3 days each) in the previous year
3. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4. Airflow limitation: after appropriate bronchodilator withhold FEV1 ,80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Allergy & Asthma NETWORK

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October 17, 2018

Steven D. Pearson, MD, MSc
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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 evidence report 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 United States.
- 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), 3 in 5 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. Furthermore, the 2016 OPEN Asthma Survey conducted by Allergy & Asthma Network revealed that >99% of severe asthma patients limited their activities of daily living due to asthma symptoms in the previous four weeks.

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

I. Lack of the Patient Perspective
ICER claims to have consulted with patient organizations for the patient perspective; however, none of the originally outlined considerations were incorporated. We believe the draft report significantly underestimates the societal burden outlined above. The cost-effectiveness analysis focuses primarily on the payer perspective without full consideration of the societal perspective. It is imperative that ICER use more patient-centered

estimates of lost productivity, indirect costs and caregiver burden. Other costs are due to the reduced quality of life that severe asthma imposes on patients living with the disease. These unquantifiable costs include the inability to engage in typical daily activities, the inability to exercise, inability to sleep, and increased student absences from school. While the report mentions several of these costs, the value of these costs is not included in the analysis.

II. Lack of Addressing the Heterogeneity of Clinical Data and Targeted Therapies

ICER assesses all biologics despite significant clinical data differences. Draft voting questions 2-4 require the review committee to assess comparative effectiveness without proper regard to the heterogeneity of data.

The draft evidence report does not explain how ICER accounted for the variability in clinical trial inclusions and 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. Moreover, draft voting questions 2-4 should be eliminated from consideration based on the lack of clarity of the comparative effectiveness provided to the committee.

In fact, the majority of studies reviewed did not even report on the factors of interest. For example:

- only two out of the 18 studies collected data on "Change in AQLQ (Asthma Quality of Life Questionnaire) and SGRQ" indicators;
- only three out of the 18 studies collected data on "Reductions in OCS (Oral Corticosteroids) Dose" as a key quality of life indicator;
- only seven out of the 18 studies collected data on annual rate of ER visits and hospitalizations;
- only nine out of the 18 studies collected data on change in FEV1 change from baseline pre/post bronchodilator.

Page 17 of the report states that: “given the residual heterogeneity across studies, we consider this analysis exploratory.” We are very concerned that patient access could be restricted based on exploratory analysis.

Allergy & Asthma Network stands ready to partner with ICER to support the value assessment and ensure cost-effectiveness of these treatment solutions. We implore the committee to consider true patient-centered outcomes rather than simply reducing asthma exacerbations or QALYs. 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 benefits both the individual patient and the healthcare system.

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

Tonya A. Winders
President & CEO

October 22, 2018

Institute for Clinical and Economic Review

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

Dear ICER:

On behalf of the members of the American Thoracic Society, I appreciate the opportunity to submit comments on draft report: Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks.

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

This is an important report, and the final report findings will likely have significant influence on forthcoming clinical practice guidelines, insurance coverage for monoclonal antibodies (MABs) for the treatment of asthma, and the selection of specific agents for the treatment of asthma. It is with this recognition of the weight that this report may carry that we urge ICER to proceed with caution, precision, and transparency.

Primary Recommendation

The ATS has significant concerns with the draft report including the selection of data used in the report, how the available data was analyzed, and the assumptions used to analyze data. We recommend that ICER address the concerns outlined in our comments and issue a second draft report for public review and comment, before moving forward with issuing a final report. We believe this iterative approach will ensure the final ICER report has the credibility to appropriately shape clinical and coverage decisions surrounding the appropriate use of MABs for the treatment of severe asthma.

General Comments

As a general principle, the ATS opposes requiring patients whose asthma is well controlled on one MAB from being forced to switch to a different one based solely on ICER's report findings. Selection of the appropriate MAB for the treatment of asthma should be left to the patient and their health care providers. While we recognize it is not the intent of ICER to require such prescription drug switching, we are concerned that the comparative findings may shape health insurance coverage policies to force patients who are well controlled on their current MAB regimen to switch to a different MAB product, even in the absence of statistically significant effects in the network meta-analysis.

The report, in its current state, is incomplete. As noted in the report, existing data was not incorporated into the report's analysis because it was received too late for inclusion (see reviewer comments on network meta-analysis). We urge future iterations of the ICER draft report to include all available data in its analysis.

The report is influenced by the patient valuation of control of daily symptoms vs avoidance of asthma exacerbations. The report notes that patients tend to value daily symptom control over exacerbation. While the meta-analyses and cost-effectiveness analysis appropriately include both outcomes, the network meta-analysis includes only asthma exacerbations. It is unclear why this is the sole outcome that was considered, particularly since the report suggests that it is the less important outcome. Both outcomes should be included in the network meta-analysis, if feasible.

The report lacks transparency. In several places in the report, statements are made about effectiveness rates and cost/benefit ratios without adequate explanation or documentation on how those estimates were developed.

Specific Comments

1. *Include all relevant medical professional statements on the management of severe asthma*.

Section 2.2 of the document – Clinical Guideline – fails to mention the ERS/ATS guidelines and GINA statement. The ICER document specifically mentions the NAEPP and NICE guidelines but does not mention the ERS/ATS guideline or the GINA guidelines in section 2.2 – although both the ERS/ATS and GINA document are referenced in the ICER report. The ATS suggested that both the GINA and ERS/ATS document can provide useful information for ICER's review of the treatment of severe asthma and should be reviewed in section 2.2 of the document. In particular, the ERS/ATS guideline includes an evidence synthesis for omalizumab, one of the drugs included in the report.

2. *The ATS has concerns with the network meta-analysis*.

The report notes, "(w)e performed a network meta-analysis in this subgroup [patients with eosinophils >=300 cells/uL] . . . but received data too late for the draft review." How did the lack of inclusion of this late data influence the results of the ICER analysis?

We are concerned that ICER, having access to this data, chose to move forward with a report that did not include the data in its analysis. We would have preferred ICER slightly delay the issuance of the draft report and included the additional data in the draft report analysis. Absent that, we recommend ICER use the newly received data to rerun the analysis and issue a revised draft report for public comment.

3. *Use network meta-analysis for both quality of life and exacerbations*.

The ATS notes with interest that exacerbation rate was the only outcome assessed via the network meta-analysis. We find it curious that after the long discussion of how patients value quality of life over exacerbations avoidance, the report did not conduct a network meta-analysis of quality of life improvements. We recommend that the report findings would be strengthened by conducting network meta-analysis for both exacerbation rates and quality of life in between exacerbations.

4. *Network Meta-analysis results may be misleading*.

Given #2 and #3 above, the ATS is concerned the results of the network meta-analysis may be misleading and potentially misinterpreted by clinicians and coverage policies. The analysis appears to favor dupilumab (table 3.12). The report authors correctly list the many limitations to the network meta-analysis findings and suggest the findings are exploratory. However, the authors should be acutely

aware that this report will be closely reviewed and likely implemented by insurance companies. Providing "exploratory" analyses in an ICER report has the potential to cause more harm than good. The mere mention of potential differences may incorrectly tip the scales in favor of one drug over the other in the eyes of clinician and coverage policies, despite the poor quality of evidence. We strongly recommend that ICER re-run the network meta-analysis with the aforementioned newly acquired data; it is our hope that this will improve the quality of ICER network meta-analysis.

5. *Figure 1.1*

The figure suggests that oral corticosteroid (OCS) use is an intermediate endpoint and not an actual endpoint. The ATS disagrees that reduction in OCS use is an intermediate end point only. For patients on daily OCS, a reduction or elimination of the OCS is a clinically and economically relevant endpoint.

6. *Control Environmental Factors and Comorbid Conditions*

The ATS notes with concern that the ICER report appears to recommend treating patients with severe asthma with allergy immunotherapy. We are curious about the evidence-base for recommending allergy immunotherapy for the treatment of severe asthma. Similarly, while we agree sinus disease is a significant problem in many patients with severe asthma, we note it is extremely challenging to treat sinus disease in patients with severe asthma, and we note lack of evidence to suggest treatment of sinus disease can help control severe asthma.

7. *Dupilumab and meta-analysis.*

The ATS notes that the ICER Report states, "We identified only one relevant trial for dupilumab for each of the outcomes (reduction in exacerbations, improvements in quality of life, reduction in oral corticosteroid dose), so no meta-analysis needed to be performed." We note that two phase 3 trials have been conducted that include OCS sparing outcomes. We believe there is sufficient evidence to include dupilumab in the ICER meta-analysis.

Reviewer Comments

The ATS asked two experts in the diagnosis and management of severe asthma to review and comment on the draft report. While many of the major themes they raised are reflected in this cover letter, the review comments also included editorial recommendations that may be of interest to ICER authors. I encourage ICER staff to carefully review the appended reviewer comments.

Again, the ATS appreciates the opportunity to comment on the draft ICER report: Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. We trust ICER will seriously consider our comments, revise the current draft and re-issue a draft report for public review and comment.

Sincerely,

Polly Parsons MD ATSF
President
American Thoracic Society

Reviewer 1 Comments

The ICER conducted a comparative effectiveness analysis of current biological therapies for severe allergic and eosinophilic asthma. A high quality systematic review of RCTs concluded that these treatments provide additional clinical benefits over the standard of care comparator. As shown in other metanalysis, biological asthma therapies have greater impact on asthma exacerbation rates and have modest effects on quality of life or lung function. Patients that are eosinophilic benefit more than those that are not, and there is no evidence that one treatment is superior to another; while the ICER analysis showed some variations in the exacerbation risk relative to placebo, between different treatments, these were not statistically different. I agree that there are significant uncertainties regarding the longer-term efficacy and safety of these products.

The cost effectiveness analysis included a quality-adjusted survival and health care costs, which were estimated for each biologic and its relevant comparators using the health care sector perspective. The Markov analysis model included analysis on exacerbation and non-exacerbation states. The results were robust to multiple sensitivity analyses. Overall, the ICER analysis found that the use of asthma biologic agents provide clinical benefit in terms of gains in quality-adjusted survival over that of standard of care alone. However, due to increased biologic treatment costs, the cost-effectiveness estimates did not meet cost-effectiveness thresholds (According to the ICER analysis, these drugs seem to priced higher than the modeled benefits). Given this finding, it is important to narrow prescription of these biological agents, to patients that are more likely to be responders (severe, eosinophilic, which have exacerbated in the past) and therefore more likely to achieve a higher value care.

Minor points

Major error on concluding paragraph on pg 29-30 where they reversed omalizumab and mepolizumab names in their paragraphs (doses, info correspond to the other drug)

Reviewer 2 Comments

I have considerable concerns regarding this document at this stage. There appears to be an inherent bias towards omalizumab primarily, with a much more liberal use and interpretation of the data than for other drugs. Mepolizumab also appears to be favored without substantial evidence to support that, and even smaller clinical trials. This is my biggest concern and focuses primarily around the use of data with omalizumab that were done in pts who would no longer meet criteria for Severe asthma, and including an open label oral CS sparing study when 3 of the other 4 drugs have actual DBPC data.

There are numerous inconsistencies (sometimes appearing to be cut and paste issues) through the document as well as many errors.

I am not qualified to analyze the QALY data. It is not likely to be in favor of any of the biologics, certainly. However, the assumptions that this analysis were based on (the 1st half of the document) would appear to be flawed, with the data to support these assumptions no ot transparently presented.

In addition there are multiple other concerns listed below.

1. The 1st figure suggests OCS use is an intermediate endpoint and not an actual endpoint. I disagree. For pts on daily OCS reduction or elimination nof the OCS IS a clinically and economically relevant endpoint
2. 2. Dupilumab gets no mention in Table 1, although it is likely to be approved within the next month. Despite this it is discussed under almost identical terms as the approved drugs throughout the rest of the document
3. Page 13 Alternative approaches would suggest allergy immunotherapy use in Severe asthma, where it is almost never recommended. Similarly although it is easy to suggest treating sinus disease which is a big problem in most severe asthma pts will improve outcomes, it is extremely difficult to treat and there are no data to suggest that treating it improves SA
4. Page 17 Why cant a meta analysis for dupi be performed? It has OCS sparing and TWO Phase 3 studies?
5. Table 3.1 as written is ok, but very confusing as written. No eos inclusion criteria
6. Page 19. IT is not at all clear how the consistent figure of 50% reduction in exacerbations across all the biologics was arrived at. The published literature would suggest the range is from 30% for omalizumab to as high as 65% for dupilumab
7. Table 3.3 I don't understand where those risk reductions came from Omaliziumab looks too good, especially when considering the studies that looked at ERS-ATS defined severe asthma. Dupilumab should be better and they should have included the Phase 2B which was considered a Phase 3 by FDA. At any rate, Dupi should not come out worse than mepo or reslizumab
8. Page 20 Typo about 3lines from bottom should be ACQ
9. Page 21 Agree that omalizumab has little improvement in FEV1, but Dupillumab should be noted as having greater improvement in FEV1. It is unclear where the dupi differences between Rx and placebo came from as they are not consistent with the published data which show anywhere from 150 to 250 ml? Table 3.6
10. The statement that the smaller improvement in FEV1 with omalizumab is s due to the fact these pts had allergic asthma is a biased statement and should be removed.
11. Table 3.7 How is it possible to show dupilmuab decreased blood eosinophils?
12. Page 24 The estimated rate of anaphylaxis for omalizumab is 0.2%. AND The estimated rate of anaphylaxis for omalizumab is 0.3%. IT cant be both. Please correct.
13. Page 25 Should not include the open label study of OCS reduction with omalizumab in comparison to the DBPC trials of dupi, benra and mepo Summary paragraph pge 26… should NOT compare the OCS dose reduction on placebo in open label study with DBPC trials. These are all short term reduction studies and it is judgment (not fact) to state that patients can reduce their doses on placebo therefore more effort is needed to reduce OCS dose before starting biologic. There are no data to support longterm dose reduction in the placebo (or treated) pts.
14. Page 26 SHould be DUPILUMAB not BENRALIZUMAB (1st paragraph)
15. Table 3.1. Where get these numbers? These are VERY different than published studies
16. Page 28 *However, we expected omalizumab to have a greater reduction in exacerbation rates.* This is biased statement and should be removed.
17. Page 29 "we judge there to be high certainty of a small net benefit for omalizumab 100 mg . SC every four weeks as add-on maintenance treatment compared with standard of care

including high dose ICS plus LABA or additional controller medications" this is yet another example of carelessness. Mepolizumab is dosed 100 mg q4 weeks, not omalizumab

18. Page 3o In addition to trials in adults, there are randomized trials supporting comparable benefits in the pediatric population No, there are not, other than for omalizumab
19. Page 30 In addition, there are suggestions of cardiovascular adverse events that may be more important in patients older than those studies in the randomized trials Again, an error. There are NO data to suggest mepo has CV effects. That issue is with omalizumab only (at least to date)
20. Page 30 benralizumab " There is moderate certainty because the randomized trials demonstrating efficacy were relatively small studies of short duration given the lifetime time horizon for potential use of benralizumab" This is not appropriate. THERE WERE 2 very large Phase 3 studies, combined around 2500 pts.
21. Comparisons of mepo with the other anti IL-5s seem biased. Mepo was first, but the clinical data are not very different IN fact, in Phase 3 studies, there are fewer pts treated with mepo than with any of the other newer biologics.
22. Page 31 dupi again this statement is inappropriate. " There is moderate certainty because the two trials were relatively small studies of short duration." Again, close to 2000 pts, studied from 6-12 mos.
23. Page 37 assumption tnat 5 mg pred without adverse events. Not true
24. Page 42 "The disutility of chronic OCS for the proportion of patients using >5 mg daily (-0.023)[55] was assumed to be equivalent to the disability-adjusted life years (DALYs) that were weighted by the proportion of chronic oral corticosteroid users who developed the following adverse events: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke." GERD, HTN and weight gain at a minimum should be added into the model
25. Page 44. I don't understand the table calculations
26. **Table 4.23. Threshold Annual Price Results** I don't understand . Clinical trials would suggest Dupi more effective than than omalizumab but omalizumab comes in with higher "allowable" :price Same with 4.24
27. Table page 107 doesn't make sense for published Lancet dupilumab study. Placebo didn't increase FEV1 by 280 ml. there was increase in FEv1 with drug of ~250 ml above placebo but that is not the way this is presented

Asthma and Allergy Foundation of America

October 22, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

To Whom It May Concern:

The Asthma and Allergy Foundation of America ("AAFA") along with four of its regional chapters (Maryland, Michigan, New England, and St. Louis) thank the Institute for Clinical and Economic Review ("ICER") for the Draft Report "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation" (September 24, 2018) and the work that went into developing it.

AAFA agrees with ICER that

- **Biologic therapy costs are too high to be an option for all asthmatics with moderate to severe, uncontrolled asthma**.
- **Because of the high costs, payers restrict access to the drugs and impose cost sharing that make biologic therapies unavailable and/or unaffordable to some patients with moderate to severe, uncontrolled asthma who could benefit from the therapies**.

We appreciate that ICER is calling attention to the biologic therapy access and cost issues that impact the quality life and sometimes longevity of life of some of the more than 25 million Americans with asthma, 12 million of whom have an asthma attack during the course of a year.[1]

However, we believe that ICER understated or overlooked some important points in its analysis, specifically that

- **People with moderate to severe, uncontrolled asthma are heterogenous – some people are significantly sicker and at more risk of serious exacerbations than others and have more to gain from costly therapies.**
- **Data suggests that the number of people receiving biologic therapies is much smaller than estimated by ICER and therefore the budget impact of new therapies is smaller than estimated by ICER.**
- **Few people with asthma, if any, will receive a biologic therapy for a lifetime.**
- **It is appropriate for society to pay a premium to save a life.**
- **Real-world healthcare data, when available, should inform asthma treatment cost-effectiveness and budget impact analyses. Inputs that more accurately reflect the patients with severe asthma and the patient perspective should be included as part of ICER's base-case findings. We identify several scenarios where cost per QALY is near or below ICER's $150,000 per QALY threshold.**

Until there are new, more effective and patient-tailored asthma treatments, asthma biologic therapies are potential life-savers for some people with asthma. We are concerned that ICER's conclusions underestimate the short-term importance of asthma biologics for certain

subpopulations of patients with asthma. We suggest that ICER more extensively test the robustness of its conclusions for at-risk subpopulations.

Asthma is a Heterogenous Disease

Asthma is a cluster of respiratory-related symptoms and pathophysiology, the multiple causes of which are unclear. People with asthma, even those classified as "moderate to severe, uncontrolled" are diverse. As described by Ray and colleagues:[2]

Asthma identifies a spectrum of respiratory-related symptoms, typically with a link to reversible airflow limitation… The term asthma does not identify any specific underlying pathobiology, but is a broad, umbrella-like term that covers multiple groupings of patient characteristics or phenotypes. While the term asthma has been traditionally used to describe a childhood onset disease associated with atopic/allergic responses, asthma can develop later in life, with minimal link to allergy. Although mild to severe disease has been identified across the spectrum of asthma, many studies now show that "severe asthma" is not a phenotype, but rather a description of a group of patients with high medical needs, whose pathobiologic and clinical characteristics vary widely.

ICER calculated cost effectiveness and budget impact using estimates of the broadest possible asthma patient population for whom biologic therapies are approved: patients ages 6 and older with moderate to severe, uncontrolled asthma. Not all of the patients are good candidates for biologic therapies. Many are non-controlled because they are non-adherent on their standard-of-care (SOC) drugs and adding biologic therapies to the mix is unlikely to increase their adherence. Poor adherence, even to inexpensive SOC treatments, is an unfortunate real-world reality of asthma control.[3]

Furthermore, while biologics are broadly approved by the FDA for moderate to severe, uncontrolled asthma, payers typically impose more stringent criteria for biologic approval. The ICER Draft Report provides asthma biologic approval policies for several payers. The policies provide potential biologic approval for patients with severe (not moderate) uncontrolled asthma who have exhausted non-oral corticoid steroid options, are taking high-dose inhaled corticoid steroids (ICS), and are having regular acute asthma exacerbations or severe-persistent symptoms.

Few People Receive Biologic Therapies

Data confirms that only a minority of patients with moderate to severe, uncontrolled asthma receive biologic therapies. Xolair was approved in 2003 and to-date the singular biologic therapy approved for patients with moderate severe, uncontrolled *allergic* asthma. Novartis reports that in 2017 Xolair's worldwide net sales were $920 million.[4] If we assume that all sales were in the US (they were not) and a year of the Xolair had a net annual cost of $28,900 per patient,[5] then the total US patients per month *did not exceed* 32,000. Similarly, the FDA estimated that over the two-year period from March 2014 to February 2016, 51,000 unique US patients had a prescription or medical claim for Xolair.[6] If we assume that the average patient had claims for 12 months[7] of Xolair in the 24 month period, then there were approximately 25,000 unique patients per month. Yet the ICER Draft Report estimates that 128,500 US patients have moderate severe, uncontrolled allergic asthma (half[8] of the 257,000[9] people with

moderate to severe, uncontrolled asthma of any kind). The other approved biologic therapies are much newer[10] and are used by even fewer of the estimated 128,500 US patients with non-allergic asthma.[11]

Clearly only a subset of the patients with moderate to severe, uncontrolled asthma are receiving biologic therapies – substantially fewer than the 27% assumed in the budget impact analysis portion of the ICER Draft Report.[12] Furthermore, because payer policies purposefully restrict access to biologic therapies, there is reason to believe that the asthma patient receiving biologic therapies is sicker and more at risk of serious exacerbations than the average patient with moderate to severe, uncontrolled asthma and therefore stands more to gain from costly drugs. Such "patient selection" may significantly change ICER's cost effectiveness calculations.

Drug Patients do not Stay on One Drug or Combination of Drugs over the Long-Term

The ICER Draft Report assumes that a patient with asthma who initiates biologic therapy will continue the biologic therapy for the remainder of his/her life with 100% adherence. While we recognize that ICER's Value Assessment Framework prescribes a lifetime horizon for value assessments, we feel that a lifetime horizon is less appropriate for asthma treatments than for treatments that potentially confer a lifetime benefit (such as vaccines). We ask that ICER consider that:

- **Asthma biologic therapies are a short-term treatment that must be re-administered in 2, 4, or 8-week intervals and "it does not appear that biologic therapy results in long-term remission of asthma."[13]**
- **Payers are most concerned with this year's and next year's costs and effectiveness, not the costs or effectiveness decades from now.**
- **There is real-world evidence that with or without biologic therapies, patients with severe asthma tend to improve over time.[14] Therefore, while severe asthma is a challenging period of time for a patient, it is not a lifetime and lifelong biologic therapy will likely not be required.**
- **In the real-world, for various reasons, patients do not continue biologic therapy indefinitely. The average Medicare Part D beneficiary receiving biologic therapy received the therapy for 7 months of 2016.[15] Studies document real-world non-adherence to biologic therapy.[16]**
- **Realistically, a person with asthma who initiates biologic therapy will likely cycle between biologics and other drugs over time.**
- **We are hopeful that new, more effective and patient-tailored asthma treatments will be developed within our lifetimes. The treatments will supplement or replace today's SOC and biologic therapies**.

Life is Precious

ICER's Value Assessment Framework requires quality-adjusted life years (QALYs) as the denominator metric of cost effectiveness analyses and suggests the maximum price that society should pay per QALY gained. Like previous commenters, we are philosophically challenged with the assumption that the death of a few people can be offset by marginal quality improvements in the life of many and that there is maximum value society should be willing to pay for the prevention of death.

Asthma is a life-threatening disease, directly causing the death of 3,600 people a year[17] and contributing to deaths from other causes.[18] The people most at risk of asthma-related death will only benefit from new, more effective and patient-tailored treatments if they survive to receive those drugs.

The sub-population of people with asthma most-at-risk of death includes children with severe, uncontrolled asthma, who have particularly severe and frequent exacerbations and a lifetime of human potential to retain or lose. Yet ICER modeled cost effectiveness assuming all people with asthma are age 46 (Table 4.1)[19] and separately varied exacerbation rates and subsequent inpatient and emergency department risk of death across relatively narrow bands of risk (Table 4.18).[20]

Real-World Healthcare Data Should Inform Real-Life Drug Coverage Decisions

ICER economic assessments primarily use epidemiological data to estimate the size of the potential patient population that will benefit from the treatment of interest, randomized controlled trials (RCTs) to estimate treatment effectiveness, and real-world data to estimate treatment costs. Epidemiological data may not be up to date or definitionally aligned with the population that is a candidate for treatment and RCTs are extremely controlled and not reflective of the real-life treatment decisions and behaviors of payer, physicians, and patients. We therefore believe that, when real-world healthcare data is available, real-world healthcare data should be used to estimate the potential patient population and treatment effectiveness.

In the above discussion, we have checked the assumptions in the ICER Draft Report against readily available real-world healthcare data and noted gaps. There is, however, much more potential of real-world data to inform ICER's and other asthma treatment value assessments. Claims and enrollment data sets, such as the US data sets prepared by CMS, IBM (formerly Truven), and HCCI, are available to researchers -- often with a year or less of reporting lag. Such data sets have been underutilized for answering critical asthma disease and treatment questions. For example, it is possible to use the data to estimate the real-world reduction in asthma exacerbations for patients taking asthma biologics compared to matched patients not taking biologics.

Data collected directly from patients can also be used as patients are the experts on how asthma and other diseases impact them. For example, in calculating the societal impact of asthma, we believe ICER underestimates the days of lost work productivity. AAFA's own "My Life with Asthma" survey estimates greater than three days of lost work in the severe asthma population. Providing greater transparency into ICER's Societal Impact calculations and scenario analyses would represent true dialogue with the patient community and make ICER's analyses more relevant.

We encourage ICER to use quality real-world data, when available, as a primary data source and would applaud ICER for using its leadership to promote more real-world analyses.

We Estimate that Biologic Therapies May be Cost Effective

While we recognize that ICER attempted to test the significance of patient selection via scenario analyses, we are not convinced that the tested assumptions describe the real-world

characteristics and treatment responses of the patients with severe asthma receiving biologic treatments and potential subpopulations thereof (such as children and young adults).

The reasonable range for any given assumption may be much larger than the range that ICER tested. Furthermore, to the extent that one assumption does not fit a particular population or subpopulation, it is likely that several other assumptions also lack fit. ICER, however, tests each assumption independently – holding all other assumptions constant – and therefor underestimates the total misestimation risk.

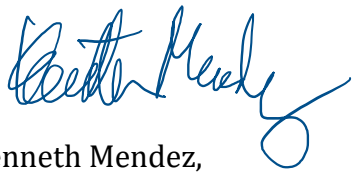
According to our estimates (see Appendices A and B), relatively modest changes in ICER's cost and utility assumptions have a significant impact on cost per QALY. For example, expanding the band of risk in SoC Utility for Non-Exacerbation (lower input) and Biologic Utility for Non-Exacerbation State (upper input) by as little as four percent brings down the associated cost effectiveness numbers (Table 4.18)[21] to ICER's target $150,000/QALY range. Similarly, a $3,210 change in the Cost for Exacerbation-Related Steroid Burst upper input brings the cost effectiveness number very close to the target $150,000/QALY range.

Likewise, simply combining a treatment responder scenario and societal perspectives, as calculated by ICER (see Appendix C) generates a best-case incremental CE Ratio range of $118,497 to $176,974; below or very close to ICER's target $150,000.

Conclusion

ICER must make sure its analyses more accurately reflect comorbidities, incremental adverse events from chronic steroid use, and the intrinsic biologic variability of the inputs associated with asthma. Greater transparency and using real-world data in ICER's modeling can make ICER's work more helpful to patients who most need these therapies. Too little is known about the multi-year natural history of asthma, the real-world use of treatments (including adherence), and the cost and efficacy of the treatments.

Sincerely,



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

cc: Susan Sweitzer, Executive Director AAFA Maryland-Greater DC Chapter
Kathleen Slonager, RN, AE-C, CCH, Executive Director AAFA Michigan Chapter
David Guydan, Executive Director AAFA New England Chapter
Marjorie Moore, Executive Director AAFA St. Louis Chapter

Asthma and Allergy Foundation of America

APPENDIX A

Table 4.18: Input Name: SoC Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.74	258,000	
	0.75	299,500	41,500
	0.76	341,000	41,500
	0.77	382,500	41,500
	0.78	424,000	41,500
	0.79	465,500	41,500
Upper Input	0.80	507,000	41,500

Revised QALY based on 1% Chg increments in Lower Input		
% Chg in Lower Input	Revised Lower Input	Revised $/QALY
1%	0.73	227,290
2%	0.73	196,580
3%	0.72	165,870
4%	0.71	135,160
5%	0.70	104,450
6%	0.70	73,740
7%	0.69	43,030

A four percent reduction in the lower input for SoC Utility for Non-exacerbation state reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Biologic Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.81	451,000	
	0.82	408,500	(42,500)
	0.83	366,000	(42,500)
	0.84	323,500	(42,500)
Upper Input	0.85	281,000	(42,500)

Revised QALY based on 2% Chg increments in Upper Input		
% Chg in Upper Input	Revised Upper Input	Revised $/QALY
1%	0.86	244,875
2%	0.87	208,750
3%	0.88	172,625
4%	0.88	136,500
5%	0.89	100,375

A four percent increase in the upper input for Biologic Utility for Non-exacerbation state reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Cost for Exacerbation-Related Steroid Burst			
	Input Range	QALY Range	$ Chg/$1k input
Lower Input	$ -	355,000	
	$ 1,172	347,778	7,222
	$ 2,172	340,556	7,222
	$ 3,172	333,333	7,222
	$ 4,172	326,111	7,222
	$ 5,172	318,889	7,222
	$ 6,172	311,667	7,222
	$ 7,172	304,444	7,222
	$ 8,172	297,222	7,222
Upper Input	$ 9,172	290,000	7,222

Revised QALY based on 5% Chg increments in Upper Input		
% Chg in Upper Input	Revised Upper Input	Revised $/QALY
5%	$ 9,631	270,510
10%	$ 10,089	251,019
15%	$ 10,548	231,529
20%	$ 11,006	212,038
25%	$ 11,465	192,548
30%	$ 11,924	173,057
35%	$ 12,382	153,567
40%	$ 12,841	134,076

A $3,210 increase in the upper input for Cost for Exacerbation-Related Steroid Burst reduces the $/QALY close to ICER's target $150k $/QALY threshold.

APPENDIX B

Table 4.18: Input Name: SoC Utility for Non-Exacerbation State	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.74	258,000	
	0.75	299,500	41,500
	0.76	341,000	41,500
	0.77	382,500	41,500
	0.78	424,000	41,500
	0.79	465,500	41,500
Upper Input	0.80	507,000	41,500

Revised QALY based on 1% Chg increments in Lower Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Lower Input	Revised Lower Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
1%	0.73	227,290	1.63	139,442
2%	0.73	196,580	1.63	120,601
3%	0.72	165,870	1.63	101,761
4%	0.71	135,160	1.63	82,920
5%	0.70	104,450	1.63	64,080
6%	0.70	73,740	1.63	45,239
7%	0.69	43,030	1.63	26,399

A one percent reduction in the lower input for SoC Utility for Non-exacerbation state and adding societal impact reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Biologic Utility for Non-Exacerbation State	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.81	451,000	
	0.82	408,500	(42,500)
	0.83	366,000	(42,500)
	0.84	323,500	(42,500)
Upper Input	0.85	281,000	(42,500)

Revised QALY based on 2% Chg increments in Upper Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Upper Input	Revised Upper Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
1%	0.86	244,875	1.63	150,230
2%	0.87	208,750	1.63	128,067
3%	0.88	172,625	1.63	105,905
4%	0.88	136,500	1.63	83,742
5%	0.89	100,375	1.63	61,580

A one percent increase in the upper input for Biologic Utility for Non-exacerbation state and adding societal impact reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Cost for Exacerbation-Related Steroid Burst	Input Range	QALY Range	$ Chg/$1k input
Lower Input	$ -	355,000	
	$ 1,172	347,778	7,222
	$ 2,172	340,556	7,222
	$ 3,172	333,333	7,222
	$ 4,172	326,111	7,222
	$ 5,172	318,889	7,222
	$ 6,172	311,667	7,222
	$ 7,172	304,444	7,222
	$ 8,172	297,222	7,222
Upper Input	$ 9,172	290,000	7,222

Revised QALY based on 5% Chg increments in Upper Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Upper Input	Revised Upper Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
5%	$ 9,631	270,510	1.63	165,957
10%	$ 10,089	251,019	1.63	153,999
15%	$ 10,548	231,529	1.63	142,042
20%	$ 11,006	212,038	1.63	130,085
25%	$ 11,465	192,548	1.63	118,127
30%	$ 11,924	173,057	2.63	65,801
35%	$ 12,382	153,567	3.63	42,305
40%	$ 12,841	134,076	4.63	28,958

A $1,376 increase in the upper input for Cost for Exacerbation-Related Steroid Burst and adding societal impact reduces the $/QALY close to ICER's target $150k $/QALY threshold.

APPENDIX C

Treatment Responder Scenario Incremental CE Ratio Cost per QALY gained including Modified Societal Perspective (vs. SoC)					
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Treatment Responder Scenario CE Cost Ratio (Table 4.21)	$205,000	$214,000	$234,000	$222,000	$269,000
Incremental QALY from Modified Societal Perspective (Table 4.20)	1.73	1.63	1.48	1.41	1.52
Adjusted Incremental CE Ratio including societal perspective	$118,497	$131,288	$158,108	$157,447	$176,974

Adding the incremental QALY from Modified Societal Perspective to the Treatment Responder Scenario brings two of the five biologic therapies below the ICER $150,000/QALY target.

[1] CDC, Most Recent Asthma Data, retrieved October 8, 2018.
[2] Ray et al, Current concepts of severe asthma, Journal of Clinic Investigation, 2016.
[3] Engelkes et al, Medication adherence and the risk of severe asthma exacerbations: a systematic review, 2014.
[4] Novartis, Full Year 2017 Product Sales, retrieved October 8, 2018.
[5] ICER Draft Report, Table 4.17.
[6] FDA, Xolair Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review, 2016.
[7] Twelve months of therapy over 24 months is an assumption based on the fact that Medicare beneficiaries have an average of 7 months of therapy during a 12 month period (see separate citation).
[8] ICER Draft Report, pg. 2.
[9] ICER Draft Report, pg. 63.
[10] Approval dates: Mepolizumab, 11/2015; Reslizumab, 3/2016; Benralizumab, 11/2017.
[11] ICER Draft Report, pg. 64.
[12] ICER Draft Report, pg. 64.
[13] ICER Draft Report, pg. 29.
[14] Chen et al, The natural history of severe asthma and influences of early risk factors: a population-based cohort study, 2016.
[15] CMS, PartD_Prescriber_PUF_Drug_Ntl_16.xlxs, retrieved October 8, 2018.
[16] Caminati et al, Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience, 2016.
[17] CDC, Most Recent Asthma Data, retrieved October 8, 2018.
[18] To et al, Asthma Deaths in a Large Provincial Health System. A 10-Year Population-Based Study, 2014.
[19] ICER Draft Report, pg. 35.
[20] ICER Draft Report, pg. 51.
[21] ICER Draft Report, pg. 51.

October 22, 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 evidence report for severe asthma therapies

Dear Dr. Pearson:

On behalf of the Institute for Patient Access and the partner organizations signed herein, I thank you for the opportunity to provide comments regarding ICER's draft evidence report 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. 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 nonprofit organization.

Impact of Severe Asthma

As detailed in ICER's draft evidence report, severe asthma is a challenging lung disease that afflicts millions of Americans. The report explicitly notes the costs that severe asthma imposes on patients, explaining that:

- Severe asthma leads to approximately 14.2 million office visits, 1.8 million emergency room visits, and 440,000 hospitalizations each year in the United States.
- Severe asthma costs society an estimated $82 billion, including $50 billion in direct medical costs, $29 billion from asthma-related mortality, and $3 billion from missed work and school.
- Individuals with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs.

Access to Clinically Effective Medicine for Severe Asthma

Mitigating the high cost of severe asthma requires, in part, access to the appropriate medications. Those include the five monoclonal antibodies indicated for the treatment of patients with moderate to severe asthma that were reviewed in this draft evidence report.

These medicines are clinically effective, as the report notes. Specifically, the report cites that the five therapies reduce asthma exacerbation rates by 50 percent.

Nevertheless, the report still finds that the drugs are not cost-effective at their current prices.

We urge ICER to reconsider this conclusion for two reasons:

1.) The draft evidence report has significant shortcomings**,** including data and methodological limitations, the inability to incorporate significant unquantifiable costs associated with severe asthma, and analyses performed in the draft evidence report that are still incomplete.
2.) **ICER's conclusion could inappropriately restrict patients' access** to appropriate and effective medications.

Exclusion of Quality-of-Life Factors

Many costs that are disproportionately borne by the uncontrolled asthma population are difficult to quantify. Yet, the methodological challenges of valuating these costs do not reduce the burden they place on patients. Ignoring many of these costs, as the draft evidence report does, significantly underestimates the benefits provided by the medicines reviewed.

Link between Uncontrolled Asthma and Comorbidities

Some of the costs that are difficult to quantify include the links between uncontrolled asthma and other comorbidities, such as psychiatric diseases and cardiac diseases that are particularly problematic for seniors with asthma. The estimated benefits from the medications do not account for a potential reduction in comorbidities.

Reduced Quality of Life

Other costs are due to the reduced quality of life that severe asthma imposes on patients living with the disease. These unquantifiable costs include the inability to engage in typical daily activities, the inability to exercise, inability to sleep, and increased student absences from school. While the report mentions several of these costs, the value of these costs is not included in the analysis.

Similarly, the ICER review considered the financial losses associated with work absences (such as lost earnings) for adults with uncontrolled asthma, but the study did not consider the losses associated with people with severe asthma being less productive while at work; nor the problems of people with severe asthma obtaining less education or requiring more social and legal services.

Lifelong Impact on Children

In section 5.2, the review acknowledges that "asthma is a life-long disease and for children suffering from severe, poorly controlled asthma, the disease may impact the entire trajectory of their lives." Yet, the costs of such impact on children are not considered in the review. With uncontrolled asthma making up 34 percent of all children with asthma, it is imperative to consider the unique costs of uncontrolled asthma in children.

Inability to Account for Ethnic Disparities

There are also important income and ethnic disparities with respect to the treatment of asthma that should be noted. For example, asthma prevalence and mortality are highly related to poverty. With respect to ethnicities, 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. However, this draft report does not account for the income and ethnic disparities of asthma.

Limited Scope of Studies Reviewed

An important limitation of the results reported in the draft evidence report is the limited scope of the data ICER reviewed. In designing the criteria for the analysis, ICER identified variables that determine the value of medicines designed to treat moderate-to severe-asthma. These variables included the number of emergency room visits, the number of hospitalizations, and several quality of life indicators typically applied to asthma patients.

In many cases, however, the majority of studies ICER reviewed did not even report on the factors of interest. For example:

- Only two out of the 18 studies collected data on "Change in AQLQ (Asthma Quality of Life Questionnaire) and SGRQ" indicators
- Only three out of the 18 studies collected data on "Reductions in OCS (Oral Corticosteroids) Dose" as key quality of life indicator
- Only seven out of the 18 studies collected data on annual rate of ER visits and hospitalizations
- Only nine out of the 18 studies collected data on change in FEV1 change from baseline pre/post bronchodilator.

Methodological Shortcomings

Beyond its data limitations, the draft evidence report also raises methodological concerns.

Specifically, page 17 of the report states that: "given the residual heterogeneity across studies, we consider this analysis exploratory." Exploratory data analyses are typically a first step in the data analysis process. Once exploratory data analyses are complete, it is common for researchers to perform more formal statistical analyses on the data set. As the report notes, however, such a formal analysis cannot be performed because of the heterogeneous nature of existing research.

Relying on an exploratory analysis introduces an unacceptable amount of uncertainty into the reported results. Further, since the clinical effectiveness results contain unknown errors, cost calculations that utilize the clinical results will also contain unknown errors. Therefore, the cost effectiveness results reported in the draft evidence report are likely inaccurate.

Timing & Incomplete Analysis

In two instances the draft evidence report notes that the analysis is incomplete, but additional analyses will be performed for the final report.

Specifically, page 26 notes:

> We requested data from manufacturers in the subgroup of patients with eosinophils ≥ 300 cells/μL and two or more exacerbations in the year prior to randomization, but received data too late for the draft review. **We will update our NMA with the additional data for the final report.** (emphasis added)

And page 28 states:

> Because of the residual heterogeneity of the underlying patient populations and the definitions of exacerbations used across trials, we consider this to be an exploratory analysis. **We hope to have more homogenous data from the manufacturers prior to the final report.** (emphasis added)

Additional data and new analyses could materially change the clinical effectiveness and cost effectiveness of these drugs as presented in the final report. Thus, *the opportunity to provide input at this stage is perfunctory*; it is an opportunity to respond to a draft that could be unrepresentative of the final analysis.

<u>If stakeholders' input bears any weight in this process, ICER would have waited and released the report for public comment after all applicable data was incorporated. Alternately, ICER could offer stakeholders the chance to respond to a more representative, second iteration of the draft.</u>

Conclusion

Based on the current iteration, this analysis provides an inaccurate, incomplete picture of the benefits created by these new biologic medicines for the treatment of asthma. IfPA

and the undersigned partner organizations urge ICER to address the concerns related to this draft evidence report.

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 Brian Kennedy at 202-499-4114.

Sincerely,

Institute for Patient Access
American Association for Respiratory Care
Allergy & Asthma Network
American College of Allergy, Asthma, & Immunology

October 22, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

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

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious, chronic, and life-threatening conditions and diseases for them to have access to vital therapies and services. Access to treatments enables those patients to have better, more productive, and longer lives. We believe access spans affordability, insurance coverage, and physical access. We are committed to engaging patients, caregivers, physicians, the media, health policy experts, payers, providers and other health professionals to foster realistic, patient-centered, solution-oriented discussions so that people facing critical medical needs can amplify their collective voice to create lasting improvements for health care in the United States. That is, our goal is to advance a balanced dialogue that illuminates the truth about health care in a just and equitable manner.

We appreciate the opportunity to provide our comments on the September 24th draft report, "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks." At the outset, we want to raise a question about the title, which unlike recent draft reports includes "Value-Based Price Benchmarks." ICER states that value-based price benchmarks "are related solely to the long-term cost-effectiveness results."[i] Therefore, putting Value Based Price Benchmarks in the report seems to tilt ICER's analytical prejudice towards economic rather than clinical outcomes. Additionally, since ICER also states that such value-based benchmarks "are being used by the pharmaceutical and insurance industries to develop pricing and coverage policies,"[ii] we are concerned that this also indicates that ICER's goal is to support the economic well-being of those companies rather than the clinical (or economic) well-being of individual patients.

This problematic anti-patient perspective is further reinforced by ICER's explanation of its methodology for value-based price benchmarks that states "the $100,000-$150,000 range for the ICER value-based price benchmark will not be shifted according to votes on 'other benefits or disadvantages' and 'contextual considerations' or on 'long-term value for money' by the independent appraisal committees"[iii] which in ICER's procedural scheme provide "clinical and policy expertise,"[iv] but unfortunately, not those of patients.

Other, specific areas of patient-focused concern with the draft report are below in sections pertaining to: Complexity of Controlling and Treating Asthma; Patient-Oriented Information and Perspectives; Uncertainties about Data and Resulting Conclusions; and Additional Points.

Complexity of Controlling and Treating Asthma
Asthma is a complex disease with many causes and triggers leading to exacerbations or worse disease. As the draft report notes, "Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells."[v]

The complexity of treating asthma is also explored in the NHLBI's clinical guidelines that lists the four components of care for people with asthma as "assessment and monitoring, education, controlling environmental factors and comorbid conditions, and medications."[vi] However, the draft report only focuses on a narrow subset of medications. Similarly, the NICE clinical guidelines note that biologics "are one piece of a comprehensive treatment plan that includes close clinician monitoring and assessment, control of patient's environment and comorbidities, and patient engagement and adherence to his/her full treatment plan."[vii]

By not fully encompassing all the treatment components of care that could improve clinical outcomes, the draft report fails to explore all the real-world concerns of patients and their care team. This is important because the "standard of care" patients are receiving needs to address all the factors that can make patient's asthma worse, cause additional exacerbations (and the need for rescue medications, including oral steroids), or prevent them from decreasing their maintenance medicines.

The draft report (and apparently the clinical trials) assume that all patients are receiving standard of care. This is important since with a great diversity of patients with asthma, we are concerned that there is also a wide diversity of what is called standard of care. Specifically, without exploring whether that care is not just "standard," but actually optimized for the individual patient, raises questions about the data. We realize that clinical improvement through overall therapeutic optimization – whether in standard of care or with a new treatment option – is not the goal of ICER's work, but we think it is important to recognize that uncertainty so that the conclusions and analytics of ICER's draft reports are not taken out of context as a way to justify anyone making clinical, access, or payment decisions for individual patients.

Patient-Oriented Information and Perspectives
As you know, Patients Rising Now is concerned with individual patient care and outcomes, as well as overall population and society issues and outcomes. And since the Asthma and Allergy Foundation of America has noted that "**there is no 'one size fits all' approach to managing asthma,"**[viii] we are very happy that the draft report recognizes what is truly important for patients: "The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is even more important to patients. They want to be able to go to work and school, exercise, and sleep through the night."[ix] But then we are very disappointed that those same clinical trial data points – that patients so clearly indicated are <u>not</u> the most important things to them – are what the draft report uses for the vast majority of its analysis and conclusions. And similarly, even though the draft report clearly illuminates patient perspectives about the balance between clinical and economic outcomes – "The two most important factors for choosing a therapy for both groups were effectiveness and

then cost. However, effectiveness was the far more important factor for patients surveyed"[x] – the report weighs the economic analytics much more heavily than patient's clinical concerns.

In addition, to better capture the breadth of patient perspectives concerning asthma treatments, we suggest that the draft report expand upon the serious consequences of long-term use of oral steroids, which are not only very serious clinically, but for patients often lead to dramatic and real life-altering adverse events.[xi] And with approximately one-third of the people in one Severe Asthma Research Program regularly using oral steroids,[xii] we would urge the draft report to highlight those consequences in greater detail, and weigh more heavily the benefits of reducing or avoiding long-term oral steroids for people with asthma.

Patients' Actual Costs

A related area of patient perspectives is actual costs to patients versus payer, insurance company or nationally aggregated costs. Asthma, like most serious diseases with a range of presentations, results in 5-10% of patients with severe asthma representing 50% of costs,[xiii] which is similar to data on the distribution of national health spending.[xiv] This range of costs translates into very different individual patient costs. This is an issue we have raised before, but we continue to find ICER's justification that it uses "a health system third party payer perspective in our base case analysis since this perspective is most relevant for decision-making by public and private payers, provider groups, and policy makers"[xv] to be a contradiction for the United States since the terms "health system" and "third party payer" cannot be joined in a meaningful way in the U.S. where multiple third party payers each have their own patient populations, coverage rules, and payment mechanisms. And those differences are very significant for patient's actual costs irrespective of the seriousness of their disease. For example, while people with Medicaid have low costs for medicines, they are not insignificant for the low-income people who are eligible for Medicaid. And for middle-income people who have high-deductible health plans those costs can be very significant. (HDHPs are increasingly common in the individual and employer-based insurance segments of the U.S. insurance markets, with 29% of employees now having high-deductible health plans.[xvi]) In contrast, for veterans' non-service connected conditions, through the VA they have a fixed-dollar co-payments of $11 per 30 day prescription, (with a $700 annual cap),[xvii] and Medicare Part D plans, which has within its complicated benefit structure the requirement that enrollees only pay 5% after reaching $5,000 in spending in the year (for 2018).[xviii] Thus, ICER continuing to treat the United States as having a singular and homogenous health care financing system – or even one that operates under a uniform set of rules is fictional or delusional.

We appreciate ICER requesting that Patients Rising Now provide them with information about "methods or estimates of patients' financial burden for different health technologies,"[xix] but the Federal government and others have conducted and published those types of analyses for years for technologies and populations concerning Medicare, Medicaid, and the VA health system. And others have conducted analyses of the costs to patients with private insurance for specific instances. Of course every disease and technology is a unique situation, which is precisely why ICER – since it presents itself as an analytical organization – should at least try to conduct this type of analysis. Just because it is challenging, does not mean it shouldn't be attempted.

Therefore, we continue to urge that ICER use a more appropriate patient-focused perspective and analytical framework that considers the pluralistic system of private and public payers in the U.S. – with rebates, discounts, and other factors that influence patient costs and access.

Uncertainties about Data and QALYs, and Resulting Conclusions

We are concerned about the extensive uncertainty of the data the draft report relies upon. For example, in the draft report there is this very telling sentence: "Because of the residual heterogeneity of the underlying patient populations and the definitions of exacerbations used across trials, we consider this to be an **exploratory analysis**. We hope to have more homogenous data from the manufacturers prior to the final report."[xx] [emphasis added] While we appreciate the candor in this statement, we think it is very, very important that this illumination not be buried in the middle of the report, but made explicit from the beginning.

Other part of the draft report concerning the systemic uncertainty of the data used in the draft report's analysis – and thus the potential significant imprecision of the draft report's conclusions – that we found troubling include:

- "There is significant heterogeneity in the FDA indications for the five drugs: allergic versus eosinophilic asthma and starting ages of 6, 12, or 18 years." (Draft report - page 17)
- "[T]here were no head to head randomized or observational trials of the five monoclonal antibodies." (page 19)
- "[A]ll five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics." (page 19)
- "If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table 3.3." (page 19)
- "When comparing the effect sizes from the meta-analyses of the individual drugs compared with placebo, the improvements in exacerbation rates and quality of life appear qualitatively similar, but this may be misleading." (page 31)

We are also concerned about ICER's use of QALY's. As noted above, because of insufficient inclusion of patient perspectives, data uncertainties, and analytical problems resulting from the data uncertainty, there is great concern that there is a significant disconnect between the analysis and conclusions. In addition, as ICER has stated, QALYs are a "widely used metric in cost-effectiveness analyses"[xxi] and that is precisely the point – the draft report presenting them as a component of clinical analysis is misleading, and we want to reiterate the conclusion of Garrison et al. that "QALYs may not always fully capture the health (or well-being) of patients, or incorporate individual or community preferences about the weight to be given to health gain - for example, about disease severity, equity of access, or unmet need."[xxii]

Additional Points

- In the draft report, clinical guidelines, and published literature, the terms "Quick Relief" and "Rescue" are used to refer to medicines for treating acute exacerbations of asthma. However, for patients with moderate or severe asthma, since acute exacerbations can lead to very

serious consequences – including death – we believe that the draft report should use the term "rescue" rather than "quick relief."

- We are puzzled by the characterization of Wellcare IL, and Aetna Better Health IL as "commercial plans" since their websites indicate that their business is only with government insurance programs, i.e., Medicare and Medicaid.[xxiii] We consider commercial insurance to be that which is paid for through premiums by individuals or companies, or which administers health benefit plans for self-insured companies operating under ERISA. We believe that this distinction should be clarified in the draft report.
- Another area of concern is the draft report's discussion of coverage policies for a medicine that is provided solely through by intravenous injection (such as Reslizumab) since it would be covered under an insurance plan's medical benefit, while the self-administrable medicines would typically be covered under a plan's drug benefit – and those differences in coverage can dramatically influence patient costs. This too should be explained in the report.
- We are confused by the opening sentence in the Clinical Guidelines section: "The U.S. Department of Health and Human Services, National Institutes of Health, and National Heart, Lung, and Blood Institute jointly release clinical guidelines for the diagnosis and treatment of Asthma." [xxiv] First, shouldn't it be "released" rather than "release" since it is something they have done in the past, and it is not an ongoing or necessarily repetitive activity? And second, these are three connected (i.e., not separate) government organizations, so stating that they jointly release[d] guidelines is misleading. Their relationships and the tense should be corrected.

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report on some treatments for people with moderate and serious asthma inadequately reflects patients' perspectives about the complexity of treatment regimens, quality of life, clinical versus economic concerns, and actual patient costs – including non-medical interventions. The continuing over-representation of medical and payer perspectives at the expense of patient perspectives in ICER's reports is an ongoing concern.

We believe patients' voices need to be a greater part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care within the pluralistic U.S. health care system. Minimizing patient perspectives and concerns continue to be a barrier to more value-based care, and movement toward a more just and equitable health care system in the United States. Removing such barriers – and addressing gender, and socioeconomic disparities in access to care and outcomes – is something that the United States can and should do better. Since some of those barriers are perpetuated by siloed or homogeneous thinking, we would hope that ICER would be part of that solution rather than continuing to be part of the problem by reinforcing payer and provider privileges for making decisions that are clearly determinantal to specific groups of individuals – particularly individuals with more serious conditions.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

[i] https://icer-review.org/blog/icer-addresses-misrepresentation-of-methods/
[ii] https://icer-review.org/announcements/price-increase-reports/
[iii] https://icer-review.org/final-vaf-2017-2019/
[iv] https://icer-review.org/about/independent-voting-committees/
[v] Draft report "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks" p. 2.
[vi] Draft report Op. cit., p. 12.
[vii] Draft report Op. cit., p 14.
[viii] "My Life With Asthma: Survey Overview," Asthma and Allergy Foundation of America, 2017
[ix] Draft report Op. cit., p. 20.
[x] Draft report Op. cit., p. 8.
[xi] http://www.asthma.partners.org/NewFiles/OralSteroids.html
[xii] "International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma," Eur Respir J 2014; 43, p 361.
[xiii] Draft report Op. cit., p. 1.
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[xv] https://icer-review.org/material/cgrp-response-to-comments/
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