INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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

Response to Public Comments on Draft Evidence Report

November 13, 2018

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Manufacturers		
AstraZeneca		
1.	Consideration for Patients: Severe asthma is a heterogeneous, complex disease with high unmet need requiring novel therapies. 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 agree that severe uncontrolled asthma is a heterogeneous health state and that asthma treatments impact patients in heterogeneous ways. Treatment price, a component of care value, is generally homogeneous and is generally agnostic with respect to patient outcomes. The report is consistent with ICER methodology and generates average estimates of long-term cost effectiveness. We provide a number of scenario and sensitivity analyses to give further context around the uncertainty in the findings.
2.	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.	Patient preferences are included with the utility estimates in the quality-adjusted life years measure. We did not differentiate across products with respect to patient preferences as the comparisons of interest were biologic plus standard of care versus standard of care alone. Productivity is included within a modified societal perspective using best-available evidence that was considered to be weak and uncertain. Patient adherence is an important issue in asthma pharmacotherapy. We used trial-based clinical evidence and therefore did not want to mix adherence evidence from the real world with that of trial-informed clinical evidence associated with high levels of adherence in the trial.
3.	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	Subsequent to the posting of the draft evidence report, all five manufacturers in this review have now shared a net-price for their biologics and these manufacturer- reported prices are used as inputs throughout the report.

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	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.	
4.	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), (see comment) we have calculated the following average annual WAC cost over a patient's lifetime for each treatment being studied. 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.	The target population in the cost-effectiveness analysis includes adults diagnosed with OUD and seeking treatment with MATs. Our objective was to establish the value of different MATs in an OUD population seeking treatment with one of the many MAT treatment options. We acknowledge that each MAT has treatment pre-requisites and these entire "treatment" pathways have been included using the decision tree prior to patients entering the Markov model in the cost-effectiveness analysis.
5.	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. 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. 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-	The estimates for the OCS sparing effects due to biologics come exclusively from randomized trials. In section 3 of the report, we specifically discuss the results of the ZONDA trial including both the reduction in OCS use and specifically highlight that despite greater reductions in OCS, patients in the trial who were randomized to benralizumab lower rates of asthma exacerbations compared with the placebo group. We added the RR for the every 8-week group to the text to emphasize the reduction. We have not included any data from non-placebo controlled or open label trials. The benefits of OCS sparing are described within the methods of Section 4. Specifically, chronic OCS is associated with disutility and large costs. Thus, a reduction in the proportion of the treated cohort who are no longer on chronic OCS results in lower costs and lower disutilities.

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	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.	
6.	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.	Thank you for pointing us to the extension trial data. We do not consider two years of follow-up to be long duration for a therapy that is likely to be used for decades.
7.	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). 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.	The quoted text comes from the section describing the NMA results in Table 3.12. The NMA results found no significant differences between drugs. The NMA has been updated to better reflect the subgroup of interest based on new data submitted by manufacturers. We have added the newly published MAIC you cite to Appendix B.

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Genentech		
1.	Increase the comparative clinical evidence rating for Xolair: 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. 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: [See letter for table]. The assessment of comparative clinical effectiveness should be updated or corrected to reflect all available evidence for Xolair.	The weight and strength of the evidence led us to the assessment of high certainty about the effect size. Thus, the rating is either A, B, C, or D (see the ICER rating matrix user's guide). We judged that the net benefit was small, rather than substantial based on the modest changes in ACQ and AQLQ and the modest reduction in exacerbation rates.
2.	*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). 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).	We agree that the XPORT data are intriguing, but they do not directly apply to the question addressed in this report - the benefits of starting biologics like Xolair. XPORT is a withdrawal of therapy trial.
3.	*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.	We agree that eosinophil response doesn't correlate with outcomes and we don't assert it's correlated with clinical outcomes. We pre-specified that we would address it in our analysis plan and feel that it is important for consistency to keep in in the revised report.
4.	*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). Pooled subgroup analyses from pivotal trials and real-world effectiveness data demonstrate meaningful benefit in older populations (>50 years of age). No new safety signals outside of the current label have been identified	The footnote to Table 2 (your real-world study meta-analysis) reports results as the change from baseline to 12 months - not long-term data. The meta-analysis stops after 24 months. In a companion publication from the same study, the authors conclude that the "Benefits of omalizumab may extend up to 2-4 years....". Many of the long-term studies you cite are small - for example, your reference number 12 reports on 7 patients treated for 7 years. We do highlight the overall robustness of the evidence for omalizumab including the longer real-world experience for the

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	based on annual safety reports submitted to regulatory bodies such as the FDA and EMA. The effectiveness and safety of Xolair have been observed after 5, 7, and up to 9 years of follow-up.	drug in our summary assessment. That is why we concluded high certainty about the net health benefits.
5.	*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. The Cochrane review pooled safety data across 25 Xolair RCTs, providing additional data to supplement ICER's meta-analysis of 7 Xolair studies.	We have added the qualitative Cochrane assessment to the section on drug discontinuation due to adverse events.
6.	*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). 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. 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. Excluding these studies from the analysis will reduce heterogeneity.	We have updated our NMA and use the pooled data from Casale 2018. We have excluded the EXTRA and EXACT studies from the updated NMA.
7.	Sufficiently and appropriately incorporate real-world evidence into the assessment of value: 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. 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). 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.	This report is consistent with ICER methodology standards. We used the clinical review to inform the clinical inputs to the economic model in terms of exacerbation signals, chronic OCS reduction, and utilities. We acknowledge the importance of real-world evidence associated with omalizumab. Another important issue in asthma is the regression to the mean. Therefore, the clinical team in correspondence with the economic team decided to not use single arm studies to inform comparative or incremental estimates in the clinical and economic review.
8.	Utilize Xolair-specific data to inform cost-effectiveness models for Xolair: It is best practice in health economic modeling to use the best available data to inform model assumptions. Xolair has data available from its own evidence base to directly inform the comparison of Xolair	Thank you for this comment. There is a balance of internal versus external validity often discussed in the clinical evidence space that also has relevance to economic study design. This report attempts to strike the balance by producing findings that can

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	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.	be interpreted across a wide and heterogeneous population while bounding the findings with scenario and sensitivity analyses. In other words, there were aspects within the economic model that did not materialize in meaningful differences across the evaluated treatments such as pooling the standard of care annualized exacerbation rates or proportion on chronic oral steroids. This pooling exercise allowed for the evidence to be more useful for policy decision making. However, we tested the impact of pooling across standard of care characteristics by adding a best-case scenario across the evaluated biologics. Therefore, these new scenarios can be useful in determining the potential impact that pooling has toward biasing the incremental cost-effectiveness findings.
9.	*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. The SOC data for Xolair was provided to ICER in prior communications.	Thank you for this comment. There is a balance of internal versus external validity often discussed in the clinical evidence space that also has relevance to economic study design. This report attempts to strike the balance by producing findings that can be interpreted across a wide and heterogeneous population while bounding the findings with scenario and sensitivity analyses. In other words, there were aspects within the economic model that did not materialize in meaningful differences across the evaluated treatments such as pooling the standard of care annualized exacerbation rates or proportion on chronic oral steroids. This pooling exercise allowed for the evidence to be more useful for policy decision making. However, we tested the impact of pooling across standard of care characteristics by adding a best-case scenario across the evaluated biologics. Therefore, these new scenarios can be useful in determining the potential impact that pooling has toward biasing the incremental cost-effectiveness findings.
10.	*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. 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.	We appreciate the suggestion to look into alternative estimates of utility for the non-exacerbation health state in the economic model. In the prior ICER report that evaluated mepolizumab, the SGRQ was used to inform the difference in utility for mepolizumab plus SOC versus SOC alone for the non-exacerbation health state. First, SGRQ has been extensively validated in asthma (see 1. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire.

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		Respir Med. 1991;85 Suppl B:25-31; discussion 33-27. 2. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. The American review of respiratory disease. 1992;145(6):1321-1327. 3. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. The European respiratory journal. 2002;19(3):398-404. 4. Bae YJ, Kim YS, Park CS, et al. Reliability and validity of the St George's Respiratory Questionnaire for asthma. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(7):966-971. 5. Nelsen LM, Vernon M, Ortega H, et al. Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. Respir Med. 2017; 128:42-49.). Second, although all biologic therapies have comparative AQLQ evidence that can be used as an alternative evidence source to estimate utilities for the non-exacerbation health state, we found the comparative AQLQ mapped utilities that yielded a smaller incremental benefit for biologics versus the SGRQ incremental benefit. Third, given that this exercise is about estimating a health state utility, one can argue that the utility estimate should be the same across all biologics (i.e., there are no known evidence sources to suggest significant preferences for one biologic versus another that would result in different biologic-treated non-exacerbation health states). Finally, the decision to use the SGRQ-mapped utility for all biologic treatments was strengthened by prior patient-level research suggesting comparable omalizumab AQLQ-mapped utility improvements versus standard of care.
11.	*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. Additionally, the proportion of responders, 60.5% is based on Xolair trial data.	We appreciate the evidence generation activities by Genentech in the omalizumab responder space. Unfortunately, the field lacks a consistent and clinically practiced definition of biologic response that is tied to continuation/ discontinuation of treatment. The lack of an actionable definition as well as a lack of trial-

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		based evidence for potential responders led us to run an evaluation of responders that was outside the base case. The uncertainty of this responder scenario is lower for omalizumab but given the interest in producing policy-relevant evidence, we reported findings for the other biologics with assumptions that similar relative signals may hold. We added language to the discussion section 4.4 to call out this out, "The uncertainty in the responder scenario findings is lowest for omalizumab given more available evidence."
12.	*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. 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.	This report is consistent with ICER methodology standards. We used the clinical review to inform the clinical inputs to the economic model in terms of exacerbation signals, chronic OCS reduction, and utilities. We acknowledge the importance of real-world evidence associated with omalizumab. Another important issue in asthma is the regression to the mean. Therefore, the clinical team in correspondence with the economic team decided to not use single arm studies to inform comparative or incremental estimates in the clinical and economic review.
GlaxoSmithKline		
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. 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	We appreciate the submission of supplementary data. We have updated our NMA using newly submitted data from multiple manufacturers specifically limited to participants with eosinophils ≥ 300 cells/µL and ≥ 2 exacerbations in the prior year. We have listed the data inputs in Appendix Table D7 when authorized by manufacturers and cited the R package used for the analysis in the descriptive section above Appendix Table D7.

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	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.	
2.	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.	See prior comment.
3.	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. Additionally, caring for someone with severe asthma is a substantial commitment, impacting family relationships and the ability to maintain care-giver employment. Coupled with the body of evidence that has demonstrated the correlation of asthma severity to direct and indirect costs, 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. We	The ICER report acknowledges the large burden within uncontrolled asthma. This burden evidence in isolation is unfortunately not helpful for the comparative estimates of cost-effectiveness as we would need to have estimates of how the burden changes with biologic treatment. In spaces where we did find evidence of changes with biologic treatment (work productivity is one example), we included such evidence in the cost-effectiveness findings. The work productivity evidence was weak and uncertain but was included within the modified societal perspective.

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	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.	
4.	*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.	Thank you for your comment. Aligning with recommendations from the Second Panel on Cost-effectiveness, we present our analyses form both a health sector, and a societal perspective. However, in accordance with ICER's policy on economic evaluations, our base case analysis has been presented only from a health sector perspective. We reserve presentation of co-base analyses (comprising both a health sector and societal perspectives) only to diseases/disorders that fall under ICER's definition of ultra-rare diseases. See ICER's modifications to our value assessment framework for reviews of treatments for ultra-rare diseases here.
5.	2. We recommend that ICER use more recent, patient-centric estimates of lost productivity, missed work/school days due to severe asthma from AAFA7 and fully account for the differences in indirect costs by disease severity, patient age, and care-giver impacts.	The work productivity evidence was weak and uncertain but was included within the modified societal perspective.
6.	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.	We agree patient perspectives are critical. The input of patient groups is evidence throughout the report; including, but not limited to, the following sections of the report: Background, Outcomes, Insights Gained from Discussion with Patients, and Other Benefits and Contextual Considerations. Moreover, patient reported outcomes (modeled through the SGRQ) are the number one driver of biologic-associated utility improvements in the economic model.
7.	Comparative Clinical Effectiveness: Key Issues Related to the Misrepresentation of NUCALA Data - (1) 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. 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.	A B rating is more robust than a B+ because of a higher level of certainty about the magnitude of the health benefit. If we were to consider the benefits of mepolizumab to be less certain, then we would change the rating to a C+. We do not consider the estimated net benefits of mepolizumab to be substantial because of the modest improvements on the quality of life scales and the modest reductions in exacerbation rates.
8.	(2) ICER must correctly characterize the health-related quality of life (HRQoL) outcomes for NUCALA. ICER	The last two sentences under quality of life in section 3 of the draft report read "The summary

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	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), the St. George's Respiratory Questionnaire (SGRQ) benefit from NUCALA exceeded the MCID. Inaccurately characterizing these data has major consequences at all stakeholder levels.	estimate for mepolizumab compared with placebo was -7.40 points (95% CI: -9.50 to -5.29). By this measure, the average patient treated with mepolizumab had a clinically meaningful improvement in quality of life, even though this was not observed with the ACQ or AQLQ." We do not think that this is an inaccurate characterization.
9.	(3) 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.	Thank you for pointing this out. We have removed the data on the AQLQ for mepolizumab from the report.
10.	(4) 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.	Please note that Table 3.12 has been updated with new data in confidence provided by manufacturers. The inputs that are not in confidence are presented in Appendix Table D7 and the methods used for the NMA are also described in the text just above Appendix Table D7.
11.	(5) 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.	In the summary section for mepolizumab in the draft report we state explicitly: "trial extension studies confirming ongoing benefits from therapy up to five years, and real-world observational studies reporting similar benefits to those observed in the randomized trials." This is why we now give mepolizumab a B rating rather than the C+ given to the other IL-5 agents.
12.	(6) 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.	Thank you for pointing out the error. We have corrected it.
13.	(7) 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. We believe this is a copy and paste error from the previous paragraph using data relevant to a different product.	Thank you again for pointing out the error. We corrected it.

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14.	(8) 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. As context, ICER should specifically acknowledge that ligand versus receptor binding has been hypothesized to affect safety of therapeutic antibodies. 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). 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).	We have added text about the different mechanism of action and eosinophil depletion.
15.	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.	We have highlighted our NMA as exploratory but have specifically limited it to the population with eos ≥ 300, at least two exacerbations in the prior year, and baseline ACQ ≥ 1.5 to minimize heterogeneity. The NMA has been updated in the final report.
16.	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.	1. We have specified our approach, included the inputs for our NMA, as well as the R package used to generate the results. 2. We have reviewed the published NMAs (see Appendix B) and highlighted the contradictory conclusions across the published literature.
17.	*Recommendations*: (1) ICER should transparently differentiate moderate asthma from severe asthma.	We have highlighted this difference in study population and FDA indications for the different drugs throughout the report.

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18.	(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]). 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. 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.)	Our NMA is intended to do just that by limiting the analysis to the more severe phenotype across the sources of heterogeneity - the group likely to derive the greatest benefit from therapies targeting type 2 inflammation. To fully account for the heterogeneity, we would need patient level data from all of the trials. Only one of the five manufacturers offered a route to access patient level data, so this was not possible. The analyses of Busse et al as well as other papers using MAIC are described in Appendix B.
19.	(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. If propensity matching fails to adequately control for confounders and effect modifiers, we recommend that ICER assess other contingencies such as outcomes regression methods.	Thank you for the suggestions. We have elected to restrict to a common subgroup rather than use techniques that are best suited to analyses with individual level data.
20.	(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.	The primary clinical benefits for the asthma cost-effectiveness model include reductions in asthma exacerbations, reductions in chronic oral steroid use, and improved day-to-day non-exacerbation asthma. All three of these signals were not considered long-term evidence but were forecasted in the same way across all of the assessed products. Namely, we held fixed, the reductions in exacerbations, chronic oral steroid use, and improvements in day-to-day asthma in order to estimate lifetime costs and health outcomes. Although we used the same evidence for all products with respect to improved day-to-day non-exacerbation asthma, a health state in the model, we used product-specific evidence to assign reductions in exacerbations and chronic oral steroid use. Within a separate response, we addressed the suggestion to use product-specific evidence for the improved day-to-day non-exacerbation asthma health state."

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21.	Suggestions to Improve Face Validity and Minimize Misinterpretation of Results: (1) 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.	Every ICER report, including this one, is reviewed by external experts. This report was formally reviewed by external asthma specialists. Details of about the people who reviewed this draft can be found on page iv of the draft evidence report.
22.	(2) 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.	Thank you for that suggestion, but we feel that the current approach to summarizing the information eases communication to the reader. We have highlighted the lack of head to head data throughout as well as the uncertainty inherent in making any comparisons between two or more of the agents.
23.	(3) 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.	The key data tables (3.3 through 3.12) all present point estimates with their 95% confidence intervals.

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24.	Comparative Cost-effectiveness Analysis (CEA): (1) 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.	We acknowledge the heterogeneity throughout the report but included the moderate asthma population because two of the five drugs have FDA indications for moderate-to-severe asthma. Scenario analyses within the economic model assess the cost-effectiveness within populations consistent with severe uncontrolled asthma and suggest findings above common thresholds.
25.	(2) 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.	There is a balance of internal versus external validity often discussed in the clinical evidence space that also has relevance to economic study design. This report attempts to strike the balance by producing findings that can be interpreted across a wide and heterogeneous population while bounding the findings with scenario and sensitivity analyses. In other words, there were aspects within the economic model that did not materialize in meaningful differences across the evaluated treatments. We appreciate the suggestion to look into alternative estimates of utility for the non-exacerbation health state in the economic model. In the prior ICER report that evaluated mepolizumab, the SGRQ was used to inform the difference in utility for mepolizumab plus SOC versus SOC alone for the non-exacerbation health state. First, the SGRQ has been extensively validated in asthma (see 1. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85 Suppl B:25-31; discussion 33-27. 2. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. The American review of respiratory disease. 1992;145(6):1321-1327. 3. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. The European respiratory journal. 2002;19(3):398-404. 4. Bae YJ, Kim YS, Park CS, et al. Reliability and validity of the St George's Respiratory Questionnaire for asthma. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(7):966-971.

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		5. Nelsen LM, Vernon M, Ortega H, et al. Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. Respir Med. 2017; 128:42-49.). Second, although all biologic therapies have comparative AQLQ evidence that can be used as an alternative evidence source to estimate utilities for the non-exacerbation health state, we found the comparative AQLQ mapped utilities that yielded a smaller incremental benefit for biologics versus the SGRQ incremental benefit. Third, given that this exercise is about estimating a health state utility, one can argue that the utility estimate should be the same across all biologics (i.e., there are no known evidence sources to suggest significant preferences for one biologic versus another that would result in different biologic-treated non-exacerbation health states). Finally, the decision to use the SGRQ-mapped utility for all biologic treatments was strengthened by prior patient-level research suggesting comparable omalizumab AQLQ-mapped utility improvements versus standard of care.
26.	(3) 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.	Thank you for your comment. As per ICER's reference case, in the absence of net prices from the SSR database for ALL considered interventions in an economic evaluation, ICER will use the FSS price. However, we also consider the use of manufacturer-provided net prices in our evaluations. As per our reference case, we apply WAC only to generics in our evaluations.
27.	Budget Impact Analysis (BIA): (1) 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 funneled 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	Thank you for your comment. In the absence of estimates measuring the prevalence of moderate asthma, we assumed that patients on long-term therapy among those with persistent asthma comprised moderate as well as severe persistent asthma patients. Our budget impact model assumes that market share for Dupixent is taken ONLY from those on biologics (27%) and not the remainder of eligible patients not on biologics, which we acknowledge is a limitation and underestimates uptake. However, we also consider 100% uptake among biologics based on

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	past 3 months. This methodology results in an underestimated patient population for Dupixent.	their individual market share, which is an overestimate of the percentage of patients who will be treated with Dupixent. It is important to note the percentage of the eligible population that can be treated before exceeding ICER's budget impact annual threshold, and what stakeholders believe the uptake of Dupixent will be.
28.	(2) 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.	See response above.
29.	(3) 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.	As part of improving its model transparency efforts, ICER has started sharing some of its models with interested stakeholders for limited time frames. Model sharing is dependent on modelers collaborating with ICER for a specific review. For this review, we are unable to share our model, but have made all methods and inputs publicly available (unless inputs were shared as confidential data with us) to aid model replication. We are happy to provide guidance on specific modeling methods or inputs which you feel required more detail to be able to replicate our model. We have also moved to rounding results since we believe that exact results are dependent on very specific input values around which there tend to be uncertainty.

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30.	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. 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.	We respectfully disagree. An argument could be made that there is insufficient evidence or that there is sufficient evidence for each of the questions. These are important policy questions that we feel should be debated in public and voted on by the panel.
Sanofi Genzyme/Regeneron		
1.	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. 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 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. 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. 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	Thank you for your comments. We have summarized all of the published ITCs for the five biologics in Appendix B. We received multiple comments that we should not include the IV formulation of mepolizumab in our analysis. We appreciate your sharing of data and have updated our analysis in the final report.

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	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.	
2.	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.	We appreciate the comment but feel that this is the most efficient way to communicate to our readers. We highlight throughout the report the heterogeneity of the trial populations and our inability to make confident comparisons between drugs.
3.	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.	We have added comments about the additional indications for dupilumab and the two other drugs that have indications beyond asthma. We also have highlighted that dupilumab is the only therapy indicated for self-administration.
4.	*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 FEV1 is an important independent risk factor for future asthma exacerbations. Dupilumab has demonstrated rapid improvements (within 2 weeks) in lung function (pre-bronchodilator [pre-BD] FEV1) versus placebo that were sustained up to 52 weeks of treatment; greater treatment effects were observed among patients with	We describe the changes in FEV1 for dupilumab in the section on surrogate markers of response and in Table 3.6. The economic model accounts for exacerbation reductions and therefore the predictive ability of lung function is an indirect approach; we took the direct approach to modeling exacerbation improvements in the economic model.

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	higher levels of type 2 inflammatory biomarkers. Furthermore, a prespecified analysis of the rate of change in the post-BD FEV1 (FEV1 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. 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.	
5.	*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. 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). Consistent with epidemiology data, in the dupilumab Phase 3 trial of moderate-to-severe uncontrolled asthma18, ~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. Based on the above rationale,	We agree that many of these drugs have the potential to improve symptoms from other diseases linked to type 2 inflammation and have stated that in the background. We have also listed the additional indications for each of the drugs beyond asthma. We do not think that it is appropriate to speculate about benefits beyond those for which the drugs have FDA approval. Despite varied findings across biologic and HRQoL measure, we estimated the utility in the non-exacerbation biologic treated health state based on a clinically meaningful change in a HRQoL measure. Thus, we believe we are giving the assessed treatments the benefit of the doubt in terms of improvements in day-to-day asthma.

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	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.	
6.	*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.	Done as noted above. We did not do this in the draft report, because we did not have PI guidance from the FDA at the time of the draft report.
7.	*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.	We acknowledge this limitation throughout the draft and revised report. We specifically highlight the differences in populations studied for the 5 drugs and warn readers not to place too much weight on comparisons between drugs. After detailing this for Tables 3.3 and 3.4 we say, "This caveat applies to all of the Tables 3.3 through 3.10, but will not be repeated for each outcome."

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8.	*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 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.	We briefly touch on this in the background section, but it is not central to the evidence report. We are focused on outcomes that matter to patients: improvements in quality of life, the ability to attend school and go to work, reductions in ER visits, hospitalizations, and the use of systemic corticosteroids. The underlying physiology is critical for biology and drug development but is not central to the focus of our Evidence Report.
9.	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.	Unfortunately, the field lacks a consistent and clinically practiced definition of biologic response that is tied to continuation/discontinuation of treatment. The lack of an actionable definition as well as a lack of trial-based evidence for potential responders led us to run an evaluation of responders that was outside the base case. The uncertainty of this responder scenario is lower for omalizumab but given the interest in producing policy-relevant evidence, we reported findings for the other biologics with assumptions that similar relative signals may hold.
10.	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. • 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.	Although some evidence exists related to treatment responders, it does not exist in ways that are consistent with US clinical practice. Further, the NICE evaluations made strong assumptions when estimating inputs associated with treatment responders and non-responders. One solution would be to estimate the incremental cost-effectiveness findings using a short-run time horizon such as one year. When doing so, we produced findings that were less favorable for biologics and therefore did not emphasize the short-run value of biologics.

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	• A large majority of previous economic models assessing asthma treatments have explicitly modeled response to treatment. 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.	
11.	• 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. • 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.	Unfortunately, the responder definitions reported by payers are not consistent and are not tied to evidence for those who respond versus those who do not. Thus, using this information within the evaluation requires strong assumptions that are not evidence-based.
12.	*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	Without evidence suggesting that history matters in this disease state, the patient-level model would yield the same results as the cohort-level model. Therefore, we used modeling frameworks consistent with other published asthma models.

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	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.	
13.	*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.	We have updated our report with the manufacturer reported net-price that Sanofi/Regeneron has subsequently submitted.
14.	*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.	Thank you for your comment. We respectfully disagree. We have presented indicated populations for each intervention in section 3 of the report.
Teva		
15.	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;	We agree that the group of patients in whom the biologics are likely to have the greatest value are those with GINA 4/5 and ≥ 2 exacerbations in the prior year. In addition, they should have eosinophils ≥ 300. We have refined our NMA

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	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) Cochrane 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.	based on data in confidence provided by manufacturers in the final report.
16.	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).	Thank you. As noted in the responses to earlier comments, we have removed the AQLQ data for mepolizumab from the revised report, including Table 3.4.
17.	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	We do not consider 2-3 years of uncontrolled follow-up to be long-term when considering a therapy that potentially will be given for decades to individuals. In addition, the median follow-up

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	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.	in Murphy 2017 was less than a year (319 and 343 days respectively) and Pahus 2018 (abstract only) describes the experience of 7 patients in France.
18.	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 (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	We have included the data submitted by TEVA in the updated NMA and there is a scenario analysis in the modeling section that utilizes the data from the NMA. The modeling team did not feel that these data should be the base case, in part because the FDA indications for the drugs do not consistently reflect this subgroup and in part because of the residual heterogeneity in the patients represented in the subgroup of the trials, which adds uncertainty beyond that reflected in the 95% credible intervals for the NMA. For the economic model, we included many scenario analyses that are consistent with the suggestions in this comment including the NMA subgroup analysis and other best-case scenarios. Further, we included a subgroup analysis of limiting the population to those who have chronic OCS as a part of standard of care.

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	inclusion in the draft evidence report in a timely manner, and well in advance of the report's release; however they were not included.	
19.	Teva respectfully requests, again, that ICER includes this definition in its analyses. • 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.	There is a scenario analysis of this subpopulation reflected in the NMA results (see Table 4.22).
20.	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).	Thank you. We have incorporated the data in our NMA and the scenario analysis that uses the results of the NMA.
21.	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.	The NMA has been updated to reflect this subgroup.
22.	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.	We are using the academic-in-confidence data in the NMA.
23.	The draft report implies a threshold for response based on increasing patient blood eosinophil levels for this patient subpopulation.	We agree and have tried to restrict the NMA to patients with GINA 4/5 asthma with 2 or more exacerbations in the prior year and at least 300 eos/µL

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	• 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.	
24.	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).	Thank you for sharing the data with us.
25.	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 FEV1." This statement is incorrect as: • Table 3.3 (ICER page 19) shows that reslizumab had the greatest reduction in clinical asthma exacerbations (CAEs).	Thank you. We have clarified the statements about reductions in eosinophil counts and outcomes.

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	• 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.	
26.	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.	Thank you. We have corrected the typo.
27.	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 respectfully disagree. The PI includes a warning about treating parasitic infections before starting reslizumab and discontinuing reslizumab for parasitic infections not responding to treatment. We agree that the risk is very low, but it has consistently been noted in the literature.
28.	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.	Thank you for pointing out the typo. We have updated both to reflect the most recent PI and have added references to the PI to clarify the source of the data.
29.	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	Thank you. We have added the boxed warning alert in the summary of omalizumab.

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	associated with reslizumab when determining its evidence rating.	
30.	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.	The primary way this is accounted for in the net health benefits is through discontinuation rates from AEs affecting the magnitude of the improvements in quality of life and asthma exacerbations in the ITT analyses of the pivotal trials. Since the majority of these reactions are mild to moderate, they have little impact on net health benefits when weighed against improvements in quality of life, reduced asthma exacerbations, and reductions in OCS dose and use.
31.	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.	The black box warnings had minimal impact on the final evidence ratings.
32.	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.	Unfortunately, the field lacks a consistent and clinically practiced definition of biologic response that is tied to continuation/discontinuation of treatment. The lack of an actionable definition as well as a lack of trial-based evidence for potential responders led us to run an evaluation of responders that was outside the base case. The uncertainty of this responder scenario is lower for omalizumab but given the interest in producing policy-relevant evidence, we reported findings for the other biologics with assumptions that similar relative signals may hold.
33.	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.	We agree with this general recommendation, but at this time, find it difficult to include within the final report due to limited evidence on treatment responders. The primary reason is that there is no agreed upon definition of response to therapy. This is a critical need that clinicians, specialty societies and researchers must address. Further, it is important to note that the ideal evidence sources associated with treatment responders would have a standard of care comparison.
34.	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	Thank you for your work in this area - please see the responses to the prior and subsequent comments for more detail.

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	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.	
35.	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.	We agree, but as noted above, there is a lack of agreement in the field on the definition of treatment response. The Bateman manuscript is an important step forward in the necessary dialog to reach a consensus definition.
36.	Applying Statutory discounts to CINQAIR utilization results in a weighted average net price of 91.5%.	Thank you for providing the discount for CINQAIR. We have now used this net price in our model.
37.	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.	Thank you for this comment. There is a balance of internal versus external validity often discussed in the clinical evidence space that also has relevance to economic study design. This report attempts to strike the balance by producing findings that can be interpreted across a wide and heterogeneous population while bounding the findings with scenario and sensitivity analyses. In other words, there were aspects within the economic model that did not materialize in meaningful differences across the evaluated treatments such as pooling the standard of care annualized exacerbation rates or proportion on chronic oral steroids. This pooling exercise allowed for the evidence to be more useful for policy decision making. However, we tested the impact of pooling across standard of care characteristics by adding a best-case scenario across the evaluated biologics. Therefore, these new scenarios can be useful in determining the potential impact that pooling has toward biasing the incremental cost-effectiveness findings.
38.	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.	The prior ICER report on mepolizumab included scenarios on short time horizons and suggested that the incremental cost-effectiveness was even higher than suggested in the base case. Although we view the shorter time horizon findings to be informative to certain stakeholders, we did not feature these findings within this report as they were covered within the prior review and other scenarios were deemed more important to

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		characterize the uncertainty in long term cost-effectiveness.
39.	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.	Given this evidence was single arm and did not include a comparator, the review team decided to not include it.
40.	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.	We have updated our NMA and now use data in confidence submitted by 3 manufacturers which greatly reduces the heterogeneity of the patients included in the NMA.
41.	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.	The responder scenario was informed by omalizumab evidence where available and cited using Norman et al 2013.
Patient Groups		
Allergy & Asthma Network		
1.	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	Thank you for your comment. We agree that lost-productivity, indirect costs, and caregiver burden are extremely important to consider when evaluating treatments for asthma. Unfortunately, much of the clinical evidence and clinical trial data does not adequately capture these considerations. To this end, ICER discusses other benefits and contextual considerations as additional considerations alongside our clinical evidence review and comparative value analysis. These are additionally captured during our public meeting, during which the Midwest CEPAC will discuss the key benefits and considerations that are relevant to these five biologics for asthma. Finally, the economic analysis includes a modified societal perspective

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	these costs, the value of these costs is not included in the analysis.	as a scenario analysis which models lost productivity.
2.	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.	We agree that this is an important limitation of the evidence base and encourage the patient and research community to agree on a standard set of measures that all studies should include to allow for more comprehensive evaluation of the value of these important therapies.
American Thoracic Society		
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.	Thank you for this suggestion. We have incorporated a summary of the ERS/ATS guidelines, as well as the GINA guidelines, per your suggestion.

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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.	We have incorporated data submitted in-confidence in our updated NMA to address this concern. We have also summarized the published NMA/ITCs in Appendix B.
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.	There were insufficient data to perform an NMA based on quality of life. This is a major limitation of the evidence base.
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.	We have highlighted that the NMA is exploratory but have more robust data for the revised evidence review. We have also summarized the published NMAs in this space. We hope that the ATS will advocate for availability of patient level data for a more robust NMA that can evaluate heterogeneity based on patient characteristics that are hypothesized to be important but have not yet been fully explored due to the lack of data transparency.
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.	We respectfully disagree. The endpoints that matter to patients are the complications of OCS use, not OCS use itself. Diabetes, infections, cataracts, osteoporosis, and the other manifold harms of OCS are the outcomes of interest.

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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.	Thanks for this comment. The section referenced in this comment is simply a summary of the guidelines issued by The U.S. Department of Health and Human Services, National Institutes of Health, and National Heart, Lung, and Blood Institute. We are not making any independent claims, we're simply outlining what the guidelines recommend.
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.	We included dupilumab in the NMA. However, we believe that there are only two phase 3 trials of dupilumab, one focused on a reduction in asthma exacerbations and the other focused on the reduction in OCS use in patients on long term OCS. Only the first is relevant for the NMA.
8.	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).	Thank you. We have corrected the typo.
Asthma & Allergy Foundation of America		
1.	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: *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	There is a balance of internal versus external validity often discussed in the clinical evidence space that also has relevance to economic study design. This report attempts to strike the balance by producing findings that can be interpreted across a wide and heterogeneous population while bounding the findings with scenario and sensitivity analyses. In other words, there were aspects within the economic model that did not materialize in meaningful differences across the evaluated treatments such as pooling the standard of care annualized exacerbation rates or proportion on chronic oral steroids. This pooling exercise allowed for the evidence to be more useful for policy decision making. However, we tested the impact of pooling across standard of care characteristics by adding a best-case scenario across the evaluated biologics. Therefore, these new scenarios can be useful in determining the potential impact that pooling has toward biasing the incremental cost-effectiveness findings. In addition, we agree that not all patients are good candidates for biologic therapies within the broadest possible asthma patient population. However, the clinical trial evidence flows into the

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	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. 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.	economic modeling and is consistent with the populations described within the FDA labeled indications. We do provide scenario analyses for subgroups of patients that are more homogeneous and found that the incremental cost-effectiveness remained above commonly cited thresholds.
2.	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. 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, 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. If we assume that the average patient had claims for 12 months 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 of the 257,000 people with moderate to severe, uncontrolled asthma of any kind). The other approved biologic therapies are much newer and are used by even fewer of the estimated 128,500 US patients with non-allergic asthma. 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. 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.	Thank you for your comment. We have calculated the number of eligible patients based on best available published evidence. We are happy to consider any published evidence you are able to share on the estimated eligible population. Additionally, it is important to focus on the percentage of eligible population that can be treated at the different price points of a specific intervention, before the total budget impact exceeds the ICER budget impact threshold.

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3.	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." • 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. 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. Studies document real-world non-adherence to biologic therapy. • 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.	Our prior mepolizumab ICER report suggested that the incremental cost-effectiveness was actually less favorable for shorter time horizons. We chose not to include biologic switching within this evaluation due to a lack of evidence to suggest differential benefits in this biologic experienced population. Without differential evidence, similar long-run cost-effectiveness findings would be produced by a model that allowed for switching but assumed the same clinical benefits for those who switched.
4.	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,	We understand that asthma is a life-threatening condition and agree that new treatments have the potential to impact patient lives. ICER uses commonly cited thresholds for cost effectiveness: we do not set those thresholds. Please refer to our Value Assessment Framework for more information about the rigorous process by which our methods are decided and refined.

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	directly causing the death of 3,600 people a year and contributing to deaths from other causes. 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) and separately varied exacerbation rates and subsequent inpatient and emergency department risk of death across relatively narrow bands of risk (Table 4.18).	
5.	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	Although we agree that real world evidence should be used in ICER reviews, we also wanted to include a comparator arm within analyses that informed measures of clinical benefit, including productivity signals. For estimation of the population sample size, we relied on epidemiologic evidence consistent with real world evidence.

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	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.	
6.	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) 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.	In the probabilistic sensitivity analyses, we vary all uncertain inputs at the same time to get an understanding of the overall uncertainty in the lifetime cost effectiveness findings.
Institute for Patient Access		
1.	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	Generic utility instruments such as the EQ5D capture signals across disease including asthma and others. Therefore, the use of utilities as a component of the quality-adjusted life year can capture measures of benefit within asthma and its comorbidities. Given that most of the utility estimation in asthma has been through mapping exercises of disease-specific instruments, we advocate for further studies using instruments such as the EQ5D to better understand the role

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	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.	comorbidities may play in estimating the value of asthma biologic therapies.
2.	*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.	We recommend these areas of potential lost productivity to be studied in ways that can attribute benefits or losses to asthma interventions.
3.	*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.	Running similar cost-effectiveness estimates for children are problematic given the limited comparative evidence specific to this subpopulation. However, if all the incremental benefits remained constant with the base case, we would produce incremental cost-effectiveness findings that would be less favorable for children due to the lower likelihood of exacerbation-induced mortality differences in this subpopulation. We agree that pediatric asthma is an important population, but we suspect that the biologic treatment cost-effectiveness evidence would not be more favorable for such a subpopulation.
4.	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.	Thank you for pointing our attention to important characteristics within uncontrolled asthma. We added a sentence to the economic model limitations section to reflect that we did not evaluate subpopulations such as those with income or ethnic disparities due to a lack of clinical evidence in these subgroups.

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5.	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.	We agree that this is an important limitation of the evidence base and encourage the patient and research community to agree on a standard set of measures that all studies should include to allow for more comprehensive evaluation of the value of these important therapies.
6.	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.	The comment about "exploratory" only applied to the network meta-analysis, which did not provide data for the base case cost effectiveness analyses. It only feeds into one scenario analysis. Thankfully, we have received data in confidence from three of the manufacturers, which allows for a more robust analysis with far less uncertainty. Note that all published network meta-analyses/ indirect treatment comparisons are summarized in Appendix B.
7.	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	As noted above, we have received additional data and have included an updated NMA in the revised evidence report.

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	data for the final report." 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." 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. 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.	
Patients Rising Now		
1.	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.	Thank you for your comments. We acknowledge that different patients receive different levels of care. For the purposes of this report, we clearly define "standard of care" as "daily inhaled corticosteroids plus at least one additional controller therapy." Due to how the biologics under review in this report are covered by insurance companies, and how clinicians prescribe them, it is very unlikely that a patient would be prescribed a biologic without first being on a daily inhaled corticosteroid and at least one additional controller therapy. For that reason, we can confidently say that the patients who would be prescribed a biologic do share our basic definition of standard of care relative to this review.
2.	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," 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." But then we are very disappointed that those same clinical trial data points –	Thank you for your comments. The economic analysis is one piece of our review and the qualitative data presented in the clinical section seeks to, among other things, compliment what cannot be captured in the economic analysis due to insufficient data. We frequently hear that patients desire information on how well a treatment improves their symptoms and whether its benefits will extend to other patient centric outcomes like ability to work, caregiver burden, etc., but these outcomes are rarely captured in clinical trials, which make it difficult to include in the economic analysis.

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	that patients so clearly indicated are not 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" – the report weighs the economic analytics much more heavily than patient's clinical concerns.	
3.	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. And with approximately one-third of the people in one Severe Asthma Research Program regularly using oral steroids, 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.	Thank you for the important comment. We highlight the many serious complications of systemic corticosteroid use in the 3rd paragraph of the background section: "chronic OCS therapy because it is associated with many long-term complications including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, muscle weakness, diabetes, cataracts, joint necrosis, and an increased risk for infections." The model incorporates the reduction in OCS due to use of the biologics and the consequent reduction in the long-term harms of OCS.
4.	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, which is similar to data on the distribution of national health spending. 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" 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	Thank you for raising this point. ICER's position on this has not changed: we use 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.

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	segments of the U.S. insurance markets, with 29% of employees now having high-deductible health plans.) 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), 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). 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.	
5.	We appreciate ICER requesting that Patients Rising Now provide them with information about "methods or estimates of patients' financial burden for different health technologies," 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.	Thank you for your comment. We acknowledge that costs vary by payer type, and whenever data specific to these different payer types is available, we will include relevant analyses, accordingly.
6.	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." [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.	We go to great lengths in multiple sections (including the very first one) to acknowledge areas of uncertainty and heterogeneity. The sentence you quote here was from section 3.3 and we're describing the uncertainty and heterogeneity of the data inputs for a specific subgroup analysis we conducted (patients with high levels of eosinophils and two or more exacerbations per year). Since the draft evidence report was posted, we have received additional subgroup data from three manufacturers just as we had hoped. As a result, our analysis in this subgroup is now much more robust with far less uncertainty. Note that all published network meta-analyses/indirect treatment comparisons are summarized in Appendix B.

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7.	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" 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."	QALYs are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value
8.	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 understand your point here and agree asthma is a serious condition. Our goal in the section you refer to is to summarize clinical guidelines and the guidelines to which you refer use the term "quick-relief medication." To accurately reflect their recommendations, we will keep the language as is.
9.	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. 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.	Thank you for this comment. We have taken this comment under advisement.
10.	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.	Thank you for this comment. The coverage section is meant to detail coverage policies, not individual patient costs.
11.	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." 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	We have corrected the tense. We feel comfortable with our use of the word "jointly."

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	organizations, so stating that they jointly release[d] guidelines is misleading. Their relationships and the tense should be corrected.	