INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Tezepelumab for Severe Asthma
Response to Public Comments on Draft Evidence Report

November 4, 2021

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#	Comment	ICER Response
Manufacturers		
Amgen/AstraZeneca		
1.	The draft report overestimates the budget impact from adding tezepelumab, which could inappropriately signal access restrictions for patients. We request ICER: revise the prevalence of severe uncontrolled asthma patients to align with published estimates (which is lower than what is reflected in the draft report), and include the use of other biologics to better reflect current utilization of asthma biologics in the US (biologic-eligible patients are overestimated in the draft report).	Thank you for your comment. We reviewed citations provided around estimating the prevalence of severe uncontrolled asthma, and the estimate of patients currently receiving asthma treatment with biologics. We have revised our eligible patient population estimate to be reflective for those who may be eligible for the treatment with tezepelumab but who are not currently taking a biologic therapy. The eligible population was reduced by removing patients eligible for and receiving treatment with already available biologics. Given changes in definition around severe asthma and uncontrolled asthma, and the uncertainty around uncontrolled asthma prevalence, we did not change the uncontrolled patient population component of our eligible population estimate.
2.	The draft report underestimates the risk of death in the calculation of the mortality risk per hospitalization, which inaccurately suggests a lower cost-effectiveness of tezepelumab and limits the external validity of the model. We request ICER update the mortality risk per hospitalization to align with observed severe asthma patients' death rates.	First, there is no direct evidence of a mortality benefit (i.e., rate ratio reduction on death) from the use of tezepelumab. Second, the mortality calculation is based on the CDC 2019 death count where asthma was the "underlying cause of death" as recorded on the cause of death section of death certificates. In our model, the probability is based on 3,524 deaths divided by the total population with severe asthma – approximately 2.2 million people in the United States. The CDC hospitalization data and mortality data are separate data sources and relied on a denominator of severe asthma patients. Therefore, the mortality calculation may overestimate asthma observed deaths per the CDC as we assigned this likelihood of death to only a subset of patients with asthma (severe asthma) and patients with moderate or mild forms of asthma may also experience hospitalizations due to asthma.
3.	In addition, it is important to note there is an overall inconsistency in the results from ICER's previous 2018 severe asthma assessment vs. the 2021 assessment.	We have made it clear not to compare the current results with the past asthma reviews.

4.	Budget Impact: The draft report overestimates the budget impact from adding tezepelumab, which could inappropriately signal access restrictions for patients. We request ICER revise the prevalence of severe uncontrolled asthma patients to align with published estimates (which is lower than what is reflected in the draft report)	See above.
5.	The proportion of severe asthma patients with uncontrolled disease in ICER's analysis is above the range of estimates in published literature. The CDC estimates the prevalence of asthma at approximately 22.5 million individuals 12 years of age and older, where (as referred to above) an estimated 5% , of adolescents and 10% , of adults, have severe asthma (2.1 million individuals). Published estimates of the proportion of severe asthma patients with uncontrolled disease range from 19.9% (≥2 exacerbations in a year) to 49.2% (based on asthma control test). ICER applies 60%, which is the proportion uncontrolled by patient report for all asthma patients, based on a patient survey regarding daytime/nighttime symptoms and short-acting ß-agonist (SABA) use, not exacerbation frequency. The vast majority of these patients were non-severe and were not receiving the intensive medication regimen used to treat severe asthma. ICER should revise the analysis, applying published estimates of the proportion of severe asthma patients in the US who are uncontrolled.	See above.
6.	We request ICER include the use of other biologics to better reflect current utilization of asthma biologics in the US (biologic-eligible patients are overestimated in the draft report).	We updated the eligible population to not include those currently on an asthma biologic. If the manufacturer were to share the planned price of tezepelumab, then we would have included other biologics in the potential budget impact estimates to assess the potential for differences in costs across treatments.
7.	The draft budget impact analysis does not reflect the current utilization of asthma biologics in the US. In ICER's 2018 Asthma Assessment budget impact analysis, ICER estimated 27% of patients with moderate to severe asthma were on biologics while 73% of the target population were on SoC alone. Most (approximately 85%) severe uncontrolled asthma patients are already eligible for one or more of the currently available biologic therapies. Approximately 15% of severe uncontrolled asthma	See above (we updated the analysis to include the suggested evidence around the proportion of patients who are currently on an asthma biologic).

	patients are not eligible for current biologics. As a result, tezepelumab will likely minimally increase the total number of patients receiving biologic therapy. Hence, it is clearly inaccurate to assume that in a world without tezepelumab, physicians would be treating all severe asthma patients with SoC alone. In the real-world study, CHRONICLE, of the 1,428 eligible patients screened for enrollment, 57% of all biologic-eligible patients were receiving biologics. The breakdown of these biologics was as follows: 50% omalizumab, 28% mepolizumab, 23% benralizumab, 8% dupilumab, and 4% reslizumab.	
8.	Mortality Risks: The draft report underestimates the risk of death in the calculation of the mortality risk per hospitalization, which inaccurately suggests a lower cost-effectiveness of tezepelumab and limits the external validity of the model. We request ICER update the mortality risk per hospitalization to align with observed severe asthma patients' death rates (which is higher than what is assumed in the model).	The mortality calculation is based on the CDC 2019 death count where asthma was the "underlying cause of death" as recorded on the cause of death section of death certificates. In ICERs modeling, the probability is based on 3,524 deaths divided by the total population with severe asthma – approximately 2.2 million people in the United States – or approximately 0.0068 probability of death per severe exacerbation. We may have overestimated asthma deaths by assigning all observed deaths to only the severe asthma subpopulation.
9.	ICER's calculation of the mortality risk per hospitalization underestimates the risk of death in the model. The value used in the model is 0.0068, which is lower than observed severe asthma patients' death rates. ICER should utilize CDC 2018 and 2019 data to recalibrate the model. The CDC reported 178,530 hospitalizations with a primary discharge diagnosis of asthma in 2018. Combined with the 3,524 primary asthma deaths reported in 2019, this suggests a risk of death per hospitalization of 0.01974.	The mortality calculation is based on the CDC 2019 death count where asthma was the "underlying cause of death" as recorded on the cause of death section of death certificates. In ICERs modeling, the probability is based on 3,524 deaths divided by the total population with severe asthma – approximately 2.2 million people in the United States – or approximately 0.0068 probability of death per severe exacerbation. Undoubtedly, some of the CDC reported hospitalizations came from those without severe uncontrolled asthma. Therefore, assigning the full hospitalization count to the small subset of patients with asthma eligible for biologics would lead to a biased estimate. However, we did assign all observed deaths to the subset of patients with severe asthma. Even with no indication from the CDC that the deaths were all derived from hospital stays or within only severe asthma, we include 0.01974 as the upper bound in the tornado diagram. Please see the updated tornado diagram.

10.	This is a critical variable that ICER's model is extremely sensitive to: the range of parameter values tested by ICER in sensitivity analyses does not capture the uncertainty in this model input, as it ignores the alternative values available in the published literature and other economic models of severe asthma. Underestimating these events limits ICER's cost-effectiveness model's external validity.	Input uncertainty around mortality is based on observed CDC estimates over the prior 20 years, including a sensitivity analysis to show results based on a probability of 0.01974. Broader increases would overestimate the number of observed deaths from an asthma exacerbation.
11.	ICER's model applies mortality risks only to exacerbations requiring hospitalizations. The Draft Evidence Report states that, "consistent with NICE analyses, we assumed that all asthma-related deaths occur from severe exacerbations." The 2021 Global Initiative for Asthma (GINA) guidelines defines severe exacerbations as exacerbations requiring emergency department (ED) attendance, hospitalization or a course of oral corticosteroid (OCS) and additionally added a lung function criterion of peak expiratory flow (PEF) or forced expiratory volume (FEV1) <60%. Furthermore, ICER's approach does not align with NICE's complete benralizumab appraisal. NICE's approach for severe asthma incorporates several factors for severe exacerbation mortality risk from OCS burst to hospitalizations. Furthermore, all of NICE's assessments of asthma biologics to date have included the risk of death for patients experiencing exacerbations with OCS burst or emergency room visits. The key difference is that ICER defines severe exacerbation as an "Asthma related event that requires a hospitalization" vs. NICE's approach, which more broadly defines severe exacerbation as "episodes in which patients require OCS for at least three days, an A&E visit or hospitalization, and have been shown to correlate with higher FeNO and a decrease in lung function.	As stated in the draft evidence report, the model was calibrated to produce the number of deaths observed by death certificate data in the United States in 2019 regardless of whether the patient experienced a hospital stay or not. The model assumes deaths occur from the severe exacerbation state and we acknowledge some patients may have died separate from a hospitalization but would have been sent to the hospital if the exacerbation was caught in time prior to death. Any change in the distribution of deaths would not add annual deaths but rather shift the distribution of deaths and yield similar results.

12.	US CDC 2015-2019 death certificate data reported that a third of all asthma-related deaths occur outside medical facilities. It is incorrect to assume that all asthma-related deaths occur within ER or hospital settings. The 2014 UK Royal College of Physicians National Review of Asthma Deaths supports this observation, estimating that 45% of asthma deaths (as concluded by an expert panel) in 2012-2013 (N=195) occurred before the individual could receive medical care. Excluding fatalities that occur outside of medical facilities misses substantial health inequities for example, in distance to health care facilities (e.g., rural versus urban areas) and heterogeneity in the timing and quality of care. This is compounded in populations which may also disproportionately suffer from asthma (e.g., LatinX and Black populations).	The link between severe exacerbation and hospitalization in ICERs model is specific to resource utilization and impacts on quality of life. We acknowledge some patients may have died separate from a hospitalization but would have been sent to the hospital if the exacerbation was caught in time prior to death. As stated previously, the model is calibrated to produce the same number of annual deaths as the CDC 2019 estimates. Any change in the distribution of deaths would not add annual deaths but rather shift the distribution of deaths and yield similar results.
13.	We suggest the following addition to the wording to voting question 5: "(i.e., ability to reduce potentially life-threatening exacerbations such as those leading to ER care/hospitalization).	Thank you, but that is not the intent of this question about contextual considerations.
14.	In terms of ICER's assessment process, we recommend going forward that ICER hold any early insights webinars after the comment submission, following the availability of the *Revised Report* to enrich the presentation with diverse perspectives.	Thanks, that's a reasonable point and a suggestion definitely worth considering. Payers are having internal deliberations earlier and earlier prior to FDA approval and so we are trying to balance the lack of ability to reflect public comment with the fact that payers are already using our draft report at that stage and moving ahead without waiting. We'll think about whether we should postpone the entire presentation or maybe keep the same timeline but include a more formal reflection in the presentation of the key concerns raised by companies throughout the course of the review on the scope and research/model protocols. Thanks for the comment; we will wrestle with how to handle it.
Genentech/Novartis		
1.	Include an additional set of scenario analyses for all asthma populations (severe, eosinophilic, and allergic) using key model inputs from the 2018 ICER economic analyses.	Given updates to evidence and therefore, approaches, we added language in the revised report that results should not be compared across asthma reviews.
2.	1. Utility value of 0.830 (0.020) for asthma without exacerbation based on the St. George's Respiratory Questionnaire (SGRQ) for all asthma biologics and 0.768 (0.015) for standard of care 2. Mean age of 46 years at treatment initiation 3. Distribution of exacerbations by type set to: 90% resulting in steroid burst, 5% resulting in ED visits, and 5% resulting in hospitalization	See previous response.

	4. Risk of asthma-related mortality for exacerbations leading to hospitalization (2.48% fatal) and ED visits (1.79% fatal) 5. Annualized asthma exacerbation rate (AAER) of 1.30 per-person per year.	
3.	ICER performed multiple assessments of asthma biologics over the years using different model inputs and assumptions across reviews, based on the evidence for approved and new asthma biologics. For example, in the 2016 and 2018 assessments, utility estimates for patients with asthma without exacerbations were consistent for all asthma biologics and were derived from the SGRQ, based on mepolizumab trial data (i.e., at 0.062 higher utility in the non-exacerbation health state compared to standard of care alone). The 2021 assessment deviates from the past approaches to estimate unique on-treatment exacerbation-free utility estimates for each biologic using data from a different questionnaire, the Asthma Quality of Life Questionnaire.	See previous response.
4.	ICER acknowledges that the utility estimate was the most influential driver of model results, as highlighted in the one-way sensitivity analyses. Further, most asthma biologics have a range of estimates for health-related quality of life impacts across randomized controlled trials, real world data, and questionnaires. Indeed, ICER has discussed this variation in utility estimates and their notable impact on CE model results in both the 2018 and 2021 draft report.	See previous response.
5.	Other important differences in key input assumptions between the 2021 and 2018 assessments include: a reduction in asthma-related mortality for severe exacerbations with an ED visit or hospitalization, a higher baseline exacerbation rate before treatment, a higher likelihood of ED visits and inpatient treatment for exacerbations, and higher mean age at the model start. While ICER seeks to address the differences in the 2021 review's analytic modeling approach and provides assumptions within the body of the draft evidence report for "Tezepelumab for Severe Asthma," it is instead the deterministic point estimates from ICER's assessments that become the core messages in press releases and summary	We have made it clear that it is inappropriate to compare the current results with results from past asthma reviews.

	documents used by the public. Not all stakeholders of ICER's assessments have health economics and outcomes research backgrounds which would allow them to better understand how changes in the assumptions from the 2018 CE model impacted the CE results for the biologics in the 2021 report.	
6.	The end user(s) may inappropriately compare the incremental CE ratio for asthma biologics in the 2021 assessment with CE results from the 2018 assessment, inaccurately concluding that the treatments in this review are less cost-effective. Adding scenario analyses that replicates the 2018 model assumptions for all asthma populations in this assessment allows for comprehensive comparisons and prevents misinterpretation of current results. Adopting this recommendation will facilitate more informed discussions by the health care decision makers as they evaluate biologic asthma therapies.	We have made it clear that it is inappropriate to compare the current results with results from past asthma reviews.
7.	Remove statements regarding incremental clinical benefits between asthma biologics from the ICER report given the absence of comparative clinical effectiveness evidence. Rationale: We agree with ICER's statement about the uncertainties in comparing biologics in the 2021 report: "Populations were not identical across the trials and standards of care have changed, raising the possibility that effects seen in a trial might have been different if used with different background therapy" [2]. Further, the report also acknowledges that there are important uncertainties introduced by the different time periods in which these therapies were assessed this difference in time, affects the background therapies, study design and outcome measurements. In addition, ICER rated the comparative evidence for tezepelumab with Xolair, in patients with allergic asthma as "insufficient" (I), the same evidence rating was given to tezepelumab with dupilumab, in patients with eosinophilic asthma. In the absence of comparative clinical effectiveness data among biologics, it is inappropriate to draw conclusions regarding the incremental clinical benefit between biologics. However, in multiple places throughout the report, ICER included comparative statements summarizing the clinical effectiveness. these summary statements can be	Thank you, but we believe we have used language that is fair to the therapies and the evidence.

	highlighted by the public without context and lead to inaccurate interpretations.	
8.	ICER risks misrepresenting the comparative clinical evidence in the assessment by making statements that imply an incremental clinical benefit between the asthma biologics, despite insufficient data to compare them. As a result, healthcare decision makers may incorrectly interpret the findings that could negatively impact patient access to valuable asthma therapies.	The Report also notes that while we are uncertain about relative harms, we have much longer experience with regard to the safety of omalizumab. Uncertainty does not preclude language suggesting possible directionality.
9.	Update the clinical efficacy input for Xolair's exacerbations resulting in ED visits (without hospitalization) in the allergic asthma scenario analysis. Specifically, use 0.397 as the rate ratio (RR) for Xolair's exacerbations resulting in ED visits (without hospitalization).	Please see updated Table E2.7 and Table E3.1.
10.	The selection of clinical efficacy inputs substantially impacts the model results and these inputs should be based on the most robust data available. In the scenario analysis for the allergic asthma subgroup as per "Table E2.7 Key Inputs for Allergic Asthma Scenario Analysis," the RR for exacerbations resulting in ED visit (without hospitalization) for Xolair is listed as 0.49 (95% CI: 0.25, 0.97), which is the value for hospital admissions and is incorrect [2]. Per Bousquet et al., 2005, "Table 5. The rate of hospitalizations and other unscheduled visits for pooled population using Poisson regression," the correct RR for ED visits without hospitalization is 0.397 (95% CI: 0.192-0.820), p-value 0.013. Use of the correct point estimate will yield a more accurate assessment of the effectiveness of Xolair in reducing exacerbations that result in ED visit.	Please see updated Table E2.7 and Table E3.1.
11.	Acknowledge Xolair's published clinical evidence among underserved racial and ethnic minority subgroups when discussing underrepresentation issues in clinical trials. We agree with ICER on the importance of evaluating the impact of asthma therapies for all patients, including racial and ethnic minority subgroups. Although there may be paucity of racial and ethnic minority patients in the trials of tezepelumab, the same is not true for Xolair. When stating "Black patients were also underrepresented in at least some trials of dupilumab and omalizumab," ICER undermines the available evidence on the effectiveness of Xolair treatment across racial and ethnic minority groups and	We reworded this sentence. It is the case that the INNOVATE trial included only 6.7% Black patients which would not be reflective of the US population, however, INNOVATE was an international trial.

	underserved populations who are disproportionately impacted by asthma in the real world.	
12.	Discussing the existing evidence for Xolair among racially and ethnically diverse populations will increase the representation, generalizability, and applicability of the findings of this assessment, potentially impacting access to asthma treatments for a real world population.	Thank you, but the focus of this report is tezepelumab. Omalizumab is a comparator.
Sanofi/Regeneron		
1.	Sanofi/Regeneron believes that the report can benefit from greater clarity in the description of type 2 inflammation in asthma as well as the role of dupilumab as a biologic that suppresses type 2 inflammatory pathways. As the report acknowledges, type 2 inflammation refers to innate and adaptive immune responses including T helper 2 (Th2) driven activation of key cytokines IL-4, IL-5 and IL-13. These cytokines lead to downstream activation of local and systemic inflammatory cells including eosinophils, mast cells, macrophages and goblet cells. In asthma, this can lead to eosinophil trafficking into tissue, increased IgE production as well as goblet cell hyperplasia and mucus production among many processes. Type 2 inflammatory asthma is present in most patients with severe asthma , and includes patients that are characterized as having “allergic asthma” or “eosinophilic asthma”. There are several biomarkers that can be used to identify patients with type 2 inflammatory asthma, including blood or sputum eosinophils, exhaled nitric oxide (FeNO), and peripheral IgE levels. Efficacy across multiple biologics has been evaluated in populations identified on the basis of these biomarkers, including blood eosinophils, FeNO and peripheral IgE.4 The subtype “allergic asthma,” has been identified by peripheral IgE levels, atopy, or other associated clinical features, and the subtype “eosinophilic asthma” has been identified on the basis of peripheral or sputum eosinophils.	As you note, there is lack of consensus around type 2 inflammation making it hard for the ICER Report to be clearer about this.
2.	However, it is important that the report recognize that there are not consensus thresholds for these biomarkers to define these subtypes, and efficacy has been demonstrated using different threshold for different biomarkers. As there is not consensus definition of this term, the preference would be to	We have tried to be clear when discussing results, however the FDA label for dupilumab refers to asthma with an “eosinophilic phenotype” and does not define the cut point.

	use precise terminology when providing results of trials, for example "patient with blood eosinophils ≥ 150 cells/ul".	
3.	While the report recognizes the efficacy of omalizumab for patients with an allergic phenotype, the dupilumab efficacy in this patient population should also be recognized.	We agree that dupilumab has shown efficacy in this population in clinical trials, however it lacks an FDA indication for this and so we chose not to discuss this in the ICER Report.
4.	Sanofi/Regeneron believe that the long-term safety and efficacy of medicines is a crucial element when assessing their value. In ICER's 2018 review of the use of biologics in asthma, it acknowledged that "there is a lack of evidence on the long-term safety and effectiveness of these drugs". However, we provided ICER with multiple references, on dupilumab's long-term data, including safety and efficacy in a population that has been exposed to dupilumab for up to three years in clinical trials.	We repeatedly comment on the existence of these data, and in particular when comparing tezepelumab with dupilumab.
5.	Page ES1 Please include appropriate references to support dupilumab long term data. Recommendation: Please update statement as follows: This is also true of dupilumab, and long-term studies of dupilumab provide additional evidence of safety.	We have added some citations.
6.	Page 8 Comment: We would suggest separating the concept of "eosinophilic asthma" from patients identified based on baseline eosinophil thresholds in order to provide greater clarity regarding which populations are being referenced. The term "eosinophilic asthma" appears in the dupilumab, mepolizumab and benralizumab indication statements, however there is not a consensus definition for which eosinophil threshold this refers to, and this phenotype may refer to patients identified by different eosinophil thresholds across different biologics. Dupilumab efficacy has been demonstrated in patients with baseline eosinophils >/= 150 cells/ul. To avoid confusion, we suggest that, when presenting data within certain patient populations, the agency use biomarker cut-offs rather than phenotype terminology so that the reader is aware of which patient population is being discussed. Recommendation: Throughout the text, when discussing subpopulations within dupilumab data please use	Please see above.

	terminology such as eosinophils ≥ 150 cells/µl, or eosinophils ≥ 300 cells/µl.	
7.	Page 8 Comment: The data for the phase 2b trial has been published for the overall population as well as 325 patients with baseline blood eosinophils ≥ 300 cells/µl. This includes an LS mean change in ACQ-5 from baseline to week 24 of -0.42 (P=0.0171) and -0.55 (P=0.0021) in the 200 mg q2w and 300 mg q2w groups, respectively. Recommendation: Please refer to the subgroup of patients with "eosinophilic asthma" as the subgroup of patients with blood eosinophils ≥ 150 cells/µl or include the results for the subgroup of patients with blood eosinophils ≥ 300 cells/µl as detailed above.	Edited wording to clarify this.
8.	Page 8 Comment: Please note, the change from baseline for the overall dupilumab 200mg q2w (-1.49), 300mg q2w (-1.45) and the placebo (-1.14) populations exceeded the MCID for ACQ-5. The MCID concept is meant to compare a change from baseline in an individual patient (or group of patients), not the difference in response between two populations. Recommendation: Delete "but smaller than MCID".	We revised the wording to make it clearer that it is the difference from placebo that was smaller than the MCID. We disagree with the idea that MCID cannot be used to examine differences between populations as that would imply that therapies for conditions with large placebo response always show benefits above the MCID even if they are ineffective.
9.	Page 9 In VENTURE, the reduction in OCS dose was greater with dupilumab than with placebo (70% vs 42%; p<0.001). More patients treated with dupilumab also had a reduction from baseline OCS dose of at least 50% (80% vs. 50%; p<0.001) and had a reduction in OCS dose to less than 5 mg/day (69% vs. 33%). Recommendation: Please note that this occurred regardless of baseline Type 2 biomarker.	Thank you, but we do not feel this clarification is necessary. It is difficult to assess eosinophil status in patients on OCS.
10.	Page D19 Comment: The primary endpoint for this trial was LS mean change from baseline in FEV1 at week 12 vs PBO in the population with blood eosinophils ≥ 300 cells/µl, and this was 0.26 (0.11, 0.40) P=0.0008 for the 200mg q2w group and 021 (0.06, 0.36) for the 300mg q2w group. It appears there may be a transcription error here as the units are incorrect Recommendation:	We revised the wording to reflect the results from week 12 and amended the wording of "high dose" and "low dose" dupilumab to "300mg q2w" and "200mg q2w".

	For the overall population the results are 200 mg q2w: 0.29 (0.03) and 0.16 (0.07-0.24) L vs PBO for 300 mg q2w: 0.28 (0.03) and 0.16 (0.07-0.24) vs PBO. Please update the text: A statistically significant LS mean difference versus placebo in preBD FEV1 was seen in the overall population for both the 200mg q2w dose (0.200 (0.11,0.28) L, p<0.0001) and the 300mg q2w dose (0.16 (0.08,0.25), P=0.0002). In the population with baseline blood eosinophils ≥300 cells/ul, the LS mean difference versus placebo in preBD FEV1 was 0.26 (0.11,0.40) L, P=0.0008 for the 200mg q2w dose and 0.21 (0.06,0.36), P=0.0063, for the 300mg q2w dose.	
11.	Page D19 Comment: Please note that in the pivotal LIBERTY ASTHMA QUEST trial, efficacy was evaluated in two dose levels, however the magnitude of effect was not directly compared between the two doses. This study was not powered to detect differences between these two doses and would therefore suggest refraining from making qualitative comparisons. Recommendation: Please revise text as follows: In patients with blood eosinophils ≥300 at baseline, both doses of dupilumab significantly improved Pre-BD FEV1 versus matched placebo: 300 mg q2w (0.47 vs. 0.22; diff 0.24; CI: 0.16 to 0.32; P<0.001) and 200 mg q2w (0.43 vs. 0.21; diff 0.21; CI: 0.13 to 0.29).	We re-worded such that the doses are not compared to each other but to placebo.
12.	Page D20 In LIBERTY ASTHMA VENTURE, a greater percentage of patients taking high dose dupilumab achieved a ≥ 90% reduction in oral glucocorticoid dose at 24 weeks (55.3% vs. 30.8%). High dose dupilumab also had a greater percentage of patients achieve ≥75% (68.9% vs. 39.3%), ≥ 50% (79.6% vs. 53.3%) and ≥ 0% (86.4% vs. 68.2%). Recommendation: Please refer to 300mg q2w dupilumab rather than "high dose." Please also note the proportion of patients no longer requiring oral glucocorticoids at week 24 was 48% vs 25% with OR vs PBO of 2.74.	We amended the wording of "high dose" and "low dose" dupilumab to "300mg q2w" and "200mg q2w" and added available data on patients off OCS at 24 weeks.
13.	Page D20 In a post hoc analysis of the phase 3 QUEST study, patients across the high type 2 biomarker subgroups (defined as patients with elevated biomarkers) had lower AAER (range: 0.16 to 0.65) compared to placebo (range: 0.86 to 2.35). Recommendation:	We specified which subgroup was being referred to.

	Please be specific about which "high type 2 biomarker subgroups" are referred to here: patients with baseline blood eosinophils ≥ 150 cells/µl, blood eosinophils ≥ 300 cells/µl, or baseline FeNO ≥ 25 ppb.	
14.	Page D20 Comment: The effect sizes are reversed: with patients with both eosinophils ≥150 cells/µl and FeNO ≥25 ppb at baseline showing an LS mean difference versus placebo of 0.33 L (95% CI 0.24–0.43 L) and 0.26 L (95% CI 0.17–0.35 L) at week 52 when treated with dupilumab 200 mg or 300 mg every 2 weeks, respectively; further this data point seems out of context. Recommendation: Please highlight that dupilumab led to lung function improvements across all populations identified by baseline type 2 inflammatory biomarkers (EOS≥ 150 cells/µl, EOS ≥300 cells/µl, or FeNO ≥ 25 ppb).	We corrected the effect sizes and added wording to highlight the improvements in pre-BD FEV1 across EOS ≥300 cells/µl and EOS≥ 150 cells/µl subgroups).
15.	Page D21 Patients in QUEST who did not meet the criteria for allergic asthma saw similar reductions across both doses versus placebo (overall: 60% and 45%; EOS ≤150: 71% and 63%; ≥300: 75% and 71%) Recommendation: Please use "EOS ≥ 150 cells/µl" instead of "EOS ≤ 150".	We resolved this error.
#	**Comment**	**ICER Response**
Clinicians		
Brian W. Carlin		
1.	Tezepelumab may offer hope of successful disease management to many patients – but only if patients have the ability to access it. It truly should be the decision of the prescriber and the patient on what treatment regimen they wish to pursue, and we urge you to consider the value that new treatments provide. ICER's reliance on the QALY is of great concern, especially when being used in an evaluation regarding asthma patients. As asthma is a chronic disease, the quality of life of patients, as defined by the QALY, is already diminished. This will lead to lower scores, even for drugs that are clinically effective, as patients with chronic diseases often cannot achieve perfect health.	This misunderstands the use of QALYs in thinking about the value of therapies. A treatment for a condition like severe asthma has the potential to raise quality of life much further than a treatment would in someone whose quality of life was already high. Patients with severe asthma are not disadvantaged by QALY-based analyses as the focus is on QALY gains due to treatment.
J. Allen Meadows		
1.	As acknowledged in the drafted report, the CDC estimates that 25 million Americans are living with	We agree.

	asthma and that 5-10% of these patients have severe, uncontrolled asthma. For this population of patients, the current standard of care often does little to manage symptoms and prevent exacerbations. This small cohort of patients consumes much of the estimated $82 billion of societal costs, costs that are only expected to grow in coming years.	
2.	While the economic burden to society is notable, the impact on individual patients should not be lost. In my experience working with patients, I find that patients with severe asthma face a significant loss in quality of life, experience difficulty sleeping, and often miss work/school.	We agree.
3.	It is also critically important to recognize that asthma disproportionately impacts certain demographics. Minority communities, specifically African Americans, Hispanic Americans and Native Americans, not only face higher rates of asthma, but higher rates of negative health outcomes due to asthma. It's important to recognize the disproportionate impact on people of color. The Affordable Care Act makes it illegal to discriminate against these groups through healthcare system design. In my opinion, your processes are inherently discriminatory against these groups.	Stating a belief that our processes are discriminatory, while inflammatory, does not make the statement accurate.
4.	In recent years a number of asthma treatments have been developed and come to market, which provide great hope for me as a doctor and also for my patients. For many patients, these innovative medicines have a striking impact on quality of life. However, asthma is a wide-ranging disease that impacts patients in a variety of ways. Despite these new medications, there are still a large number of patients who struggle to control their symptoms.	We agree.
5.	Tezepelumab is unique to these treatments, as it has a different mechanism of action. As a TSLP inhibitor, tezepelumab works higher in the inflammation pathway. Due in large part to positive results in Phase II trials, tezepelumab was granted "breakthrough" status by the FDA. However, the FDA has not completed their review. I urge you to reconsider issuing a recommendation without the full complement of data. The addition of this treatment to those currently available could prove valuable to many patients. Despite the recent improvement in asthma treatments, there is still a significant unmet need amongst severe,	Our report does not issue recommendations at this stage. We believe we have adequate access to the available data except as where specifically noted (such as in the subgroup of patients with both non-allergic asthma status and low eosinophils) where the manufacturer did not provide subgroup data.

	uncontrolled asthma patients. Tezepelumab could go a long way to help satisfy that need.	
6.	ICER's continued reliance on the quality adjusted life year is of great concern. The idea behind the QALY, placing a price tag on the value of living a year of health, is inherently flawed. The usage of QALYs is also discriminatory in nature. For a patient who is disabled, they will be unable to achieve a maximum score on the QALY scale, as they cannot achieve the highest "quality of life". Similar issues arise for patients of chronic conditions, such as asthma. Treatments targeted at patients whose potential for health is diminished due to chronic conditions may be given a lower QALY score. Because of these concerns, Congress has banned the QALY in cost-effectiveness reviews by the Medicare program.	As discussed above, this misunderstands how QALYs are used. The analyses focus on QALY gains due to treatment, not QALYs. The potential QALY gains due to treatment are greater (not less) for those who begin at a lower functioning status. We also report on the equal-value of life years gained (evLYG) for those who prefer an alternative measure to QALYs gained.
7.	While ICER notes that the QALY is a commonly used metric in cost-effectiveness analyses, it's important to recognize that the QALY does not evaluate clinical analysis. Garrison et al. went as far as to say that the QALY does not always capture the health or well being of patients. It also fails to incorporate factors such as disease severity, equity of access, or unmet need and I urge you to recognize its limitations.	We agree that economic analyses do not adequately capture all such factors and include in our report a section on Potential Other Benefits and Contextual Considerations.
8.	Many argue that there are no better measures of quality adjusted life years. By analogy, this is like saying since we don't have any boats without massive holes in the hull, we should sail in this one with the smallest holes, since we will not sink as soon. I'd say build a better boat and stay on shore until then. To many of us, your use of QALY renders your report of no value.	This is an interesting analogy as US healthcare drowns under the costs of manufacturers setting drug prices with no objective measures of value.
#	**Comment**	**ICER Response**
Patient/Patient Groups		
Asthma and Allergy Foundation of America		
1.	Despite the overall positive conclusion about tezepelumab's effectiveness, we are concerned that the draft report reflects inaccurate assumptions about potential use, undervaluing quality of life and overestimating potential uptake. As we noted in 2018 comments on ICER's review of biologic therapies for asthma, only a relatively small proportion of patients with moderate to severe asthma receive biologics, and typically only for a short duration. Furthermore, it is important	We believe that reducing exacerbations has value, but that a treatment which improved daily quality of life as well would have even greater value.

	not to underestimate the value of biologics that can address exacerbations that may lead to death.	
2.	ICER's review also seems to understate the importance of the new possibilities tezepelumab raises for treatment. It appears likely that tezepelumab will not have a phenotype restriction, making it effective for asthma with either allergic or eosinophils phenotypes, or mixed phenotypes. It would also be the only biologic therapy for T2-low asthma (i.e. non-allergic and non-eosinophilic). AAFA considers the emergence of treatments for patients with no similar options to be particularly important for our community.	It remains uncertain how well tezepelumab works in patients without T2 asthma, but we agree it may have such a label.
3.	AAFA is also concerned that the draft report seems to reach a conclusion regarding cost effectiveness of the product despite unknown pricing information. The report acknowledges that "[p]ricing for tezepelumab is not yet known but at anticipated prices the treatment will not reach traditional thresholds considered cost-effective in the US market." Basing this conclusion on "anticipated prices" is premature. As we stated regarding ICER's review of peanut allergy treatments in 2019, conducting a review prematurely risks limiting access – or creating fears about limited access among people who could potentially benefit from this drug – when adequate information is not yet available. We urge caution in this area until additional information about pricing can be determined and analyzed.	ICER will certainly revisit these statements if the actual price of tezepelumab is within our HBPB range.
4.	We also recommend that ICER modify the Questions for Deliberation and Voting so "yes" and "no" are not the only responses available for a committee vote. Given the early review of this therapy by ICER but before FDA review and long-term data availability, ICER should reflect this nuance in the voting questions for example by adding "NA" for not applicable or another selection that does not force the committee into binary voting choices.	Thank you, our voting questions have gone through many iterations and will likely change again in the future.
5.	We do appreciate that, consistent with our earlier recommendation, the draft report notes that most clinical trials, including those for asthma drugs, disproportionately enroll white participants, even though asthma is more prevalent and has more serious effects among Black Americans and other	Thank you, we have tried to do this in this report and intend to continue to do so in future reports.

	ethnic minority groups. We encourage ICER in future reports and analysis to continue to, at a minimum, strive to detail the representativeness, or lack thereof, of clinical trial data, and discuss how any lack of representation may impact the analysis. The draft also makes clear that a treatment that benefits people with asthma will be particularly impactful for those minority populations that are most impacted. As noted in our earlier correspondence with ICER, AAFA is deeply concerned about racial and ethnic disparities in asthma, rooted in a broad range of social determinants that affect individual and community risk. The most affected communities are, in many ways, most in need of effective treatments, and we urge ICER to continue to note where such impacts may occur.	
American Association for Respiratory Care		
1.	Tezepelumab has been granted Priority Review by the U.S. Food and Drug Administration. because it believes the biologic, if approved, would offer significant improvements in the safety or effectiveness for the treatment of severe asthma when compared to standard applications. Of concern to the AARC, and respiratory therapists who treat the disease, is the fact that patients with severe asthma are commonly prescribed the same treatment modalities as those who suffer mild or moderate asthma, although severe asthma imposes more life-threatening symptoms. That is why unfettered access to this new and promising biologic is mandatory for patients with severe asthma who face twice the risk of emergency visits to the hospital and an increased risk of mortality.	Multiple stakeholders will likely participate in decisions affecting access to tezepelumab. Among the most important stakeholder actions will be the price chosen by the manufacturer.
2.	It is also important to note that asthma compounds health disparities, especially among Black Americans and those living below poverty levels and exposed to environmental triggers. Access to a new biologic with promising results of significant improvements over current treatments offers the option to give patients of all backgrounds and races a better chance of managing severe asthma.	The Report specifically highlights this issue.
3.	As we understand the process, ICER uses a “health economics” approach in determining whether a new drug is worth the cost. While clinical trials data and available pricing information are taken into consideration, we are concerned that an	ICER’s health economic approach focuses very heavily on quality of life.

	analysis that relies too heavily on quantitative data does not account for the quality of life that matters most to patients, such as the ability to work, attend social functions, and enjoy time with family and friends. Treatment modalities can't be a "one size fits all" compromise. People living with severe asthma, along with their family and caregivers, are daily burdened, even frightened, by the persistent and often unpredictable impact of symptoms.	
Institute for Patient Access/Allergy & Asthma Network		
1.	As the draft evidence report notes, clinical trials indicate that tezepelumab is an efficacious treatment that uses a different mechanism of action. As reported in Allergic Living: in a large Phase 3 clinical trial, the biologic drug tezepelumab was able to reduce asthma exacerbations by 56% over a year in adult and teen patients with severe, uncontrolled disease. The rate of reduction is considered clinically meaningful. While reporting on the results of its Phase III trial, AstraZeneca noted that tezepelumab is "the only biologic medicine to consistently and significantly reduce AAER [annualized asthma exacerbation rate] in a broad population of severe asthma patients irrespective of baseline eosinophil count. Based on these positive clinical results, tezepelumab is a new and valued treatment option for patients, especially for patients living with severe uncontrolled asthma. Just as asthma impacts people differently, existing treatment options serve some patients better than others. Some people's asthma conditions are mild or moderate, and intermittent symptoms may be well controlled by the current standard of care. Others live with severe asthma, which may or may not respond to the current standard of care. For those who don't respond to existing treatments, their asthma may progress to a more severe or uncontrolled state. And, while asthma symptoms have an impact on patients' lives regardless of severity or frequency, severe asthma in particular can reduce quality of life and hamper patients' ability to sleep, maintain mental health, exercise, stay focused at work or school, or participate in social or extracurricular activities. These considerations are complicated by the reality that asthma is a chronic disease that will often	Thank you for your comment.

	impact people over their entire lives. The severity of the disease tends to worsen as people age, which can be complicated by waning efficacy of patients' current treatments over time. The fact that current treatments are controlling patients' asthma symptoms today does not guarantee that their symptoms will be well controlled tomorrow. Existing medications, including targeted biologic therapies, prove valuable and effective for many asthma patients. Through increasing efficacious treatment options by introducing a new mechanism of action, tezepelumab increases the likelihood that patients and their clinicians can find an effective regimen to control the disease and its symptoms – reducing dangerous or expensive exacerbations, added physician appointments and visits to the ER.	
2.	as a new medicine with a novel mechanism of action, tezepelumab represents an important addition to the asthma community's treatment options. While the value of expanding treatment options is difficult to quantify, it is imperative that these considerations be documented in the final evidence report.	We believe the report highlights both the unmet need (even with tezepelumab) and the likely expansion of the population likely to benefit from therapy.
3.	These considerations are particularly important for people living with severe asthma and for whom the current standard of care is ineffective, including people with severe uncontrolled asthma. As noted in the draft evidence report, the CDC estimates that 25 million Americans are living with asthma, and that patients with severe uncontrolled asthma represent an estimated 5-10% of total asthma cases. These figures suggest that there are currently between 1.3 million and 2.5 million people in the United States living with severe uncontrolled asthma. Severe uncontrolled asthma meaningfully reduces patients' quality of life and, in extreme cases, can even be fatal. In fact, severe uncontrolled asthma is recognized as a "major unmet medical need" by the medical community. Based on the current clinical trial results, tezepelumab will help fill this major unmet medical need. If properly applied to the small share of patients with severe uncontrolled asthma, the total societal cost estimates cited in the draft evidence report provide a useful	We agree.

	benchmark for understanding the potential value of tezepelumab. As the draft evidence report documents, the total societal costs are an estimated $82 billion, inclusive of direct medical costs, asthma-related mortality, and missed work and school. As with most diseases, however, these societal costs are not evenly distributed across all patients. Instead, a small minority of patients bear a disproportionate share of these costs. In the case of asthma, it is the patients living with severe uncontrolled asthma who bear a disproportionate share of the costs.	
4.	Worth noting, the health and economic burdens of severe and uncontrolled asthma are projected to significantly grow in the future, increasing still further the value of an efficacious treatment. Looking at the costs of uncontrolled asthma over the long-term, Yaghoubi et. al. estimated the 20-year direct costs to be $300.6 billion, or a total economic burden of $963.5 billion when indirect costs are included. The researchers expect American adolescents and adults to "lose an estimated 15.46 million QALYs over this period because of uncontrolled asthma. Assuming the costs associated with asthma-related mortality and missed work and school are due to severe asthma, patients living with uncontrolled severe asthma account for $57 billion of the total costs of asthma, or per-patient costs up to nearly $44,000. These substantial per-patient costs signify the high value of an efficacious medicine that can control or lessen severe asthma symptoms and help lower the current costs borne by severe asthma patients and their families. The cost-effectiveness analysis should explicitly account for the $44,000 in per-patient costs due to severe uncontrolled asthma when evaluating the value of tezepelumab. It is, consequently, imperative that the final evidence report incorporate these higher but more applicable per-patient costs estimates and acknowledge the reality that the costs associated with severe uncontrolled asthma will likely increase significantly without access to an effective treatment.	Thank you for the suggestion. Unfortunately this poster isn't specific enough on the breakdown of costs. The model works by assigning event-based costs to hospitalizations, ED visits, and oral steroid bursts, among other unit costs. Without resource utilization estimates broken down into separate parts, we would be double counting. However, our estimates are close to the direct cost estimation from the poster that is cited. First, for those on an asthma biologic, the cost of the biologic is the leading factor in annual per-patient costs. Those costs are included in the model. A crude calculation from our analysis shows approximately $12K per year per patient in direct non-biologic treatment costs when using the denominator of severe asthma patients cited previously in this report. We acknowledge indirect costs can be a challenge to estimate and we used a recent nationally representative analysis on indirect costs in asthma that included both time missed from school and work.

5.	The draft evidence report should also more fully account for the reality that African American, Hispanic and Native American communities bear a larger burden from asthma than do other demographic groups. Some of the troubling trends include: • Black Americans are nearly 1.5 times more likely to have asthma, five times more likely to visit the emergency room due to asthma, and three times more likely to die from asthma compared to white Americans • Puerto Ricans are twice as likely to have asthma and have a nearly three-fold higher rate of asthma-related deaths than the broader Hispanic and white populations in the United States • Native Americans are nearly twice as likely to experience asthma symptoms every day and have a 10% higher risk of death from chronic lower respiratory diseases relative to white Americans.	Thank you, we have added mention of the effects on Puerto Ricans and Native Americans to the Report. The Report already describes the burden on Black Americans.
6.	In evaluating the value of tezepelumab for people with severe and uncontrolled asthma, the disproportionate impact of asthma on people of color is an important consideration. We urge ICER to account for these impacts in its final report.	See previous response.
7.	The lifetime cost estimates do not appear to account for the temporary nature of product exclusivity. Even if the draft evidence report's assumed price were accurate in the short term, the price for the medicine should be expected to decline over time once product exclusivity expires. For instance, as GoodRx has noted, while the average cash price for branded Advair was $496 in 2018, "the lowest GoodRx price for the most common version of generic Xopenex HFA is around $32.39."	Dynamic price changes in the future are not currently recommended for inclusion in cost-effectiveness analyses in the United States. Incorporation of future pricing given exclusivity changes would add additional assumptions to the model that are difficult to predict or validate. Price increases beyond inflation have been commonly observed for other branded treatments while we do not include such potential increases in price within our analyses. Further, we are estimating the present value of costs and health outcomes to make decisions now, not in the future.
8.	As with other chronic diseases, the costs of asthma medication will stretch across a lifetime. Since the average market exclusivity period is around 12 years, it is reasonable to expect the price of the tezepelumab to decline over time, which will significantly reduce the expected lifetime treatment costs. Lower lifetime treatment costs will meaningfully alter the cost-effectiveness of tezepelumab, even at the assumed price. The final evidence report could offer a more realistic outlook were it to account for competition's impact on	See previous response.

	medication costs over the relevant study timeframe.	
Partnership to Improve Patient Care		
1.	ICER takes its baseline inputs from placebo rates from randomized clinical trials (RCT) not from real world data – this makes the model unrepresentative of real-world settings. The annual probability of an exacerbation of 1.82 per year was taken from the RCT placebo arms. We know that RCT populations are typically far healthier than the actual indicated population for the treatment. In the case of asthma, this is particularly concerning as communities of color are typically underrepresented in RCTs, and there are major racial disparities in the burden of asthma in the United States. A recent report by the Asthma and Allergy Foundation of America found that non-Hispanic Black Americans are almost three times as likely to die from asthma-related causes than non-Hispanic white Americans.	We agree that patients participating in clinical trials may have fewer comorbidities and better outcomes than patients who will receive a therapy after approval. As a result, we encourage real-world randomized trials. However that does not mean that baseline exacerbation rates are predictably higher in the real world. ICER recently examined RWE for rates of exacerbation in patients treated with prophylaxis for hereditary angioedema, and baseline exacerbation rates were much lower than in the clinical trials. For example, recent real-world evidence with over 1800 asthma patients from CHRONICLE study was used for our distribution of asthma exacerbations (mild, moderate, severe). CHRONICLE was a prospective and non-interventional study. The mean rate per patient-year was less than 1 and in the highest severity category (severe asthma + FeNO > 50) was 1.88 or about what we are using in the model from the cited trials in this review.
2.	Recent studies designed to estimate the real world rate of exacerbation in a severe asthma population have showed a much higher rate of exacerbation, ranging from 2.68-3.97 per year; 2.195 - 2.687 per year; 2.7 per year; 4.92 per year; and as much as 8.3 per year. All of these studies suggest a baseline exacerbation rate of at least 50% higher than that used by ICER and some suggest a rate greater than 400% higher than that used in the ICER model. This reliance on RCT data, which does not include a representative population of asthma patients, leads to a model that underestimates the burden of the disease and as such an underestimate of the value of any incremental treatment effect.	See above.

3.	PIPC continues to express concern with ICER's consistent use of the Quality-Adjusted Life Year (QALY). PIPC has consistently voiced concern with ICER continuing to rely on the QALY in its assessments despite its discriminatory implications for people with disabilities. In addition to its discriminatory impacts for people with disabilities, traditional cost-effectiveness assessments relying on the QALY have similarly discriminatory implications for communities of color, which bear a heavier burden of disease in asthma.	We appreciate the concerns about relying solely on QALYs. They are only one component of the value assessment that is complemented by an alternative measure, equal-value of life years gained. Many of the issues you raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.
4.	Most cost-effectiveness assessments rely on data from RCTs (issues with which we have touched on above) and health utility preference weighting surveys, which rely on inputs from primarily Caucasian populations. These assessments are largely based on outcomes to the "average" patient and do not account for patient subgroups. This means key components like social determinants of health are not captured, and ultimately treatments that may be very effective for minority populations can be undervalued.	Evidence on the effectiveness of tezepelumab within minority populations was lacking. The primary purpose of the model is to estimate the average health gains for a group of patients as well as the average costs rather than to predict or describe all potential heterogeneity across patients and time. That said, the model also includes various sensitivity analyses and scenario analyses to help assess potential variance in the model projections.
5.	The model makes the likely incorrect assumption that the reduction in risk of exacerbation at 52 weeks seen in the RCTs is the peak of the treatment's effectiveness. Several studies have shown that the impact of continued biologics use improves over time. Effectiveness (particularly reduced exacerbation rates) improves year after year for at least four years. This is not a factor that has been incorporated into the model, which only assumes the rate achieved in the RCT at year one.	We are unaware of evidence on tezepelumab's effectiveness beyond the 52-week trial endpoint. Future evidence may be incorporated into the Interactive Modeler and considered in a future evidence update.
6.	The choice of disutility for exacerbations used in the ICER model is an underestimate. ICER calculated the disutility of an exacerbation from a study undertaken in the UK, which estimated that the health state utility of an asthma patient without exacerbation was 0.89, an exacerbation that did not lead to hospitalization would have a utility of 0.57, and an exacerbation that led to hospitalization a utility of 0.33. This would mean the disutility of a non-hospitalized exacerbation is -0.32 (0.89-0.57) and the disutility of an exacerbation that leads to hospitalization is -056 (0.89-0.33).	Please re-read the referenced Lloyd et al. 2007 paper and in particular the "Mean change from baseline" column from Table 2. We use the appropriate estimates for those patients with a mean "utility change" over four weeks.

7.	Yet, the ICER model uses a disutility of 0.1 and 0.2 for these two states, despite referencing this study as its source. It seems the cause of this error is misinterpretation of the data. A fourth column in table 2 of Lloyd (2007) represents the mean change in utility over the course of the data collection period and the estimates for this fall over time within states was 0.1 and 0.2 respectively. We believe these data were mistakenly used as estimates of mean disutility for exacerbation without hospitalization and exacerbation with hospitalization in the model.	See previous response. Mean utility change is appropriate for the modeling analysis and has been referenced in multiple publications in asthma modeling.
8.	In addition, the study also states that these utilities represent the mean for the patients over a one-month period for which data was collected. The ICER model applies these utilities for just 2 weeks (a single model cycle), so even if the disutilities used were correct, they would be providing half of the absolute disutility associated with the exacerbations themselves. Taking into account both of these elements, the ICER model underestimates the disutility of exacerbation, and the absolute disutility for an exacerbation in the model is approximately one sixth of what it should be. As net benefit in the model is based largely on the rate and severity of exacerbations this means the incremental gain in health utility is likely to be six times higher than those calculated by the ICER model.	Given the study estimated the change in quality of life over a one-month period, it is unclear what the same utility estimates would be if Lloyd et al. assessed quality of life at 2 weeks instead of 4 weeks. However, this was a function of the study window and did not necessarily represent the length of an exacerbation. ICERs cycle length is consistent with prior asthma models and does not limit patients to having one exacerbation or one severity level over the course of the model.
9.	First, PIPC urges ICER to review the technical components of the model to ensure it is providing accurate results. Second, PIPC cautions ICER about the use of a QALY-based cost-effectiveness analysis relying on RCT data to evaluate treatments for asthma. It is likely that this will underestimate their benefit for patients and people of color and continue to exacerbate health disparities already experienced by asthma patients.	The model was reviewed by both internal teams and the manufacturer of tezepelumab. The model estimates both the effectiveness over a lifetime, total costs, and other outcomes including responders and equal-value of life years gained and therefore is not limited to a QALY-based evaluation.

#	Comment	ICER Response
Clinical Societies		
American College of Allergy and Asthma Immunology		
1.	First and foremost, since tezepelumab has not been approved by the FDA, we do not believe that the cost assumptions are valid, nor is it possible to compare to other biologics given differences in protocol design and lack of long-term efficacy and safety for tezepelumab. Furthermore, the FDA requires that measures of exacerbation reduction be included in the clinical trials which ICER apparently feels is not an accurate measure. We feel this review, prior to FDA approval, is premature, as we need to gain experience with tezepelumab before these kinds of documents are produced and endorsed by organizations.	Tezepelumab will have a price and be used clinically once it is approved by the FDA. Typically it is felt that evidence needs to have been generated prior to therapies being given to patients outside of clinical trials.
2.	We are also very concerned about the way information is presented regarding comparing the efficacy of tezepelumab to dupilumab or omalizumab. Without a head-to-head comparison study, this presented summary remains speculative and hypothetical. Rather than drawing hypothetical comparisons, it may be more suitable to present the data supporting the efficacy and safety of tezepelumab and highlight examples from the cost-impact of the previously FDA-approved biologics.	ICER concluded that the evidence was insufficient to compare these therapies.
3.	Finally, we are very concerned with the continued use of the quality-adjusted life year (QALY) and the Equal Value of Life Years Gained (evLYG) in commenting on a treatment prior to approval by the FDA and availability for use of the drug for a larger population outside of the clinical trials. Asthma is a complex, multifaceted disease with multiple phenotypes that leads to significant impact on quality of life and morbidity and mortality, especially among disadvantaged populations. We are aware that ICER is aware that these measures may lead to inappropriate application by policymakers (third-party payers) and urge that the "Safeguard Language to Ensure the Ethical and Appropriate Use of QALY-Based Analysis" be highlighted in the final document.	As discussed above, the QALY can be expected to perform well capturing benefits (or lack thereof) of a treatment for severe asthma. ICER's safeguard language applies to all work produced by ICER including this Report.

American Thoracic Society		
1.	The report includes the relevant published clinical trials of tezepelumab for the treatment of asthma.	
2.	The decision to compare tezepelumab to the comparator dupilumab as representative of the four currently approved treatments for eosinophilic asthma (dupilumab, mepolizumab, benralizumab, and reslizumab) is reasonable, as these agents have had similar clinical benefits in phase III clinical trials.	
3.	The clinical benefit of Tezepelumab for the treatment of patients with severe asthma is likely greater than the ICER report recognizes. We note there are very few safe and effective treatments for patients with severe asthma. We further note that data from PATHWAY published separately that looks at the proportion of patients that had significant improvements (above the MCID) in ACQ and AQLQ, which showed that 12% and 13% more patients had significant improvements in ACQ and AQLQ respectively compared to placebo. This provides more patient relevant data and counteracts the statement in the ICER report that "improvement in daily symptoms and quality of life are relatively small.	It is not surprising that over a distribution of outcomes, more patients would have improvements greater than the MCID with tezepelumab. Clinical trial results tend to look at averages and clinicians are making decisions for individual patients. Half of patients will be expected to have responses better than the mean response in a trial.
4.	Patient and Caregiver Perspective section includes statements that the ATS believes should be revised. Section 2 on "Patient and Caregiver Perspectives" contains the sentence "Symptom relief, asthma control, and quality of life matter much more to patients than a reduction in asthma exacerbations." This is a problematic statement that is not logical in the framework of the NIH asthma guidelines. Asthma control has two domains: reduction of impairment (reduction of symptoms and of ongoing need for rescue treatments; maintaining normal activity levels) and reduction of risk (prevention of exacerbations, acute health care utilization; minimization of medication side effects). "Asthma control" cannot be separated from prevention of asthma exacerbations. The ICER report to some extent seems to downplay the importance of preventing asthma exacerbations. Based on ATS asthma experts experience with patients, patients care a great deal about preventing asthma exacerbations, which are frightening, dangerous, require prednisone with its side effects, lead to ER visits, lead to missing work or childcare challenges,	We have repeatedly heard from patients, in our work on this Report, on prior reports, and as part of the coreAsthma project, that focusing on exacerbations in severe asthma (which typically occur a few times per year) can miss the burdens of daily symptoms. We have tried to reflect what we heard from patients on this issue.

	etc. We further note that for patients with severe asthma, exacerbations are likely more severe, more expensive and last longer than exacerbations experienced by patients with mild or moderate asthma. CER's executive summary statement "Additionally, as with other biologic therapies, improvements in daily symptoms and quality of life are relatively small" downplays the benefit that biologics provide to some patients with severe asthma.	
5.	ICER should adjust the Tezepelumab rating. ICER rates the net health benefit of tezepelumab added to standard of care (SOC) versus SOC alone as C++. The ATS disagrees and recommends ICER change the rating to B+. The PATHWAY and NAVIGATOR trials show that tezepelumab + SOC is clearly superior to SOC alone in preventing asthma exacerbations. This is either a B or an A, depending on how much one values the prevention of asthma exacerbations. If one splits the difference, it's a B+. We note, per figure 3.1, a C++ rating encompasses "comparable net benefit." The PATHWAY and NAVIGATOR trials exclude the possibility – with 95% certainty – of a comparable net benefit between tezepelumab+SOC and SOC alone. None of the C ratings are compatible with the evidence.	ICER ratings deal with net health benefit, which includes harms. Tezepelumab would have a higher rating if there were no concerns about harms. As discussed in the Report, new biologic therapies are often found to have harms that were unanticipated at the time of FDA approval. Frequently ICER has given a "P/I" rating in this situation, but because of the lack of therapies for many patients with severe asthma overall net harm from unanticipated adverse effects seemed sufficiently unlikely that ICER raised the evidence rating to C++.
6.	The economic analyses appear to be thoughtful and rigorous, but they do not recognize the clinical reality that some patients with severe asthma experience clinical benefit from a particular biologic therapy while others do not, even though they may have similar clinical features. If a patient does not improve after 3-6 months on one agent, physicians often switch the patient to a different asthma biologic agent. If none of the biologics result in observed benefits, the use of biologics is discontinued. With this "trial and error" approach, clinicians attempt to find the right therapy that works for a specific patient. It does not appear that the analysis of incremental costs over the "lifetime" time horizon accounts for the possibility that MDs may do a good job at tailoring therapy by "trial and error" such that patients incurring the lifetime incremental cost are fewer in number than the models predict and potentially are receiving greater benefits than the models predict. Importantly, Tezepelumab appears to provide somewhat broader efficacy than the	We acknowledge the limited evidence around responder analyses. In our scoping period, we requested additional information on responders that would flow directly into the model. Unfortunately, there was no supply of information that would be helpful for a full responder scenario. However, we do present a cost per responder analysis result and we encourage readers to review that result.

	previous biologics based on biomarker criteria. Thus, it is likely that there may be fewer "mistakes" made on initial prescribing.	
7.	The discussion in Uncertainties and Controversies may understate the effectiveness of biologics for the treatment of severe asthma. Biologics for the treatment of asthma, with their simpler regimens, may have an advantage with many patients who for complex systemic reasons have difficulty accessing routine care or adhering to complicated daily multi-drug regimens. As the report mentions, the results from these clinical trials may not be generalizable to routine practice but would be expected to have even greater benefits in routine practice where adherence and follow up frequency is more realistic.	Thank you, we have edited the section on Potential Other Benefits to reflect this issue.
#	**Comment**	**ICER Response**
Other		
Paul Langley		
1.	In the asthma model, there is no direct elicitation of ordinal preference scores (in this case the EQ-5D-5L) from patients; rather a linear transformation (utility mapping) of the ordinary least squares form: EQ-5D-5L = 0.14 + 0.12 AQLQ where AQLQ is the Asthma Quality of Life Questionnaire score (no other information on the model fit is provided which is unfortunate) EQ-5D-5L scores are ordinal and lack a 'true zero'. They cannot be used in a multiplicative mode to create QALYs as the authors of the asthma model proceed to do. Unless, of course, ICER and the expert simulation model group makes a further assumption, as ICER believes, that these EQ-5D-5L ordinal preferences are a ratio measure in disguise. ICER has two options: (i) to withdraw the assumption driven simulation model for asthma pricing; or (ii) to clam that, by assumption, the AQLQ actually creates interval scores and that the mapping algorithm creates "true" ratio EQ-5D-5L preferences. Under (i) ICER would recognize the limitations imposed by fundamental measurement and that the QALY is mathematically impossible while, under (ii), ICER would admit its models rest on assumptions and nothing more and are not intended to meet the standards of normal science. My inclination would be that ICER will take option (ii) under the defense that 'everyone else does it'; which is not only weak but demonstrably false. There are many activities which	Thank you, your concerns are noted. As we have expressed before, we (and most health economists) are confident that changes in the EQ-5D (and other multi-attribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale. The dead state represents a natural zero point on a scale of health-related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead. We do not find that this lacks face validity. We also appreciate the concerns about relying solely on QALYs. They are only one component of the value assessment, and many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.

	people partake in, yet not ones we would wish to emulate. After all, we can hardly quibble over an imaginary assumption driven simulation model if the authors introduce further assumptions to deny the axioms of fundamental measurement. What is one further assumption among the many that drive the ICER imaginary simulation?	
Phylliscia Gibson		
2.	As a respiratory therapist (RT) and asthma educator (AEC certified) at a major children's hospital in the South, the cost of severe asthma is more than a few days in our Pediatric ICU. Our facility has several services for children with severe asthma and their families. These services range from an outpatient asthma clinic to an intense and stressful hospitalization. Let's take a look at a family with a child with severe asthma who is having an asthma attack. For many asthmatics an attack often begins as a result of the common cold. So many of us take for granted something as simple as the common cold because it's just a cold right? The child presents to a hospital, urgent care center or doctors' office with status asthmaticus. They treat the child as best they can and then we get a call to our call center to dispatch an ambulance to transport the child to our specialty hospital. A nurse and RT (full transport ambulance or flight team) are dispatched. We service outside facilities if the child has to be intubated or if the child is just not getting any better. Upon arrival to the outstanding hospital, the RT and RN work vigorously to help him breathe. Fighting for time and to get the child stable, the RN and RT administer continuous breathing treatments, Heli-ox, steroids, if not already started, and magnesium. They Intubate if necessary. This could also mean physically pushing on a patients' chess to get air out of his lungs. Many kids also come straight to our emergency room via outside ambulance. Upon arrival to the children's hospital emergency department or direct admit to Pediatric ICU we continue to monitor and assess the patient for progress or deterioration. If they're still in respiratory failure despite conventional ventilation, we'll attempt High Frequency Oscillation Ventilation (HFOV). What a pneumothorax? We'll attempt Isoflurane. Our facility uses a one-on-one RT for	Thank you for sharing your story.

	isoflurane administration for the first 24 hours. It requires close monitoring of the patient's blood gasses and temperature. Inhaled isoflurane is an anesthesia gas that acts like a bronchodilator in the most severe cases of asthma. Last but not least, ECMO- Extra-Corporal Membrane Oxygenation. This requires several units of blood, a surgeon, and bedside on call OR team. We have to preserve more than lung tissue, at this point the kids' fragile brain sets them up for anoxic brain injury. This timeline can occur sometimes in a matter of hours of reaching our doorstep to several weeks in the ICU. Not only do we treat the child, the parents may also require attention from lack of sleep and not eating. Many families use continuous or intermittent FMLA to spend time and help with their child's recovery. The child loses time from school due to hospital stay and follow-up appointments. The specialty doctors for this child includes a pediatric pulmonologist, asthma-allergy specialist, and in some cases ENT (Ear, Nose, Throat). Finally, when discharge is on the horizon, that's when we start working on prevention of future asthma status asthmaticus. Every patient that is admitted to our hospital presenting with asthma has to attend an asthma class. If they get admitted 5 times, they come to asthma class 5 times. We discuss the medicines and alternatives plus an Asthma Action Plan. Sadly, I will have a mom in my class crying that their baby was started on a biologic and insurance, for whatever reason, stopped covering the injections. They would do great on Omalizumab and then their entire world comes crashing down when they stop covering the injections and their child is back in the PICU with the same scenario. I often ask parents to take care of their own mental health as well as take care of their child. I highly recommend meditation to families and patients. As a healthcare worker it is difficult to come home and release from such frustrating circumstances. Not all kids end up in the hospital due to noncompliance of drugs. For some, it can be a factor of not having money for daily meds after insurance pays their part. It's no secret that the more medicines we have for asthma, the more choices parents have, the better chance of adherence to an asthma regimen. The cost goes down! While injection biologics are not cheap, it	

	pales in comparison to the cost of the story mentioned above. The amount of time, money, and resources for severe asthma has to start with prevention.	