# Tezepelumab for treating severe asthma [ID3910]

## A Single Technology Appraisal

## Addendum #1

## EAG Review of Company's Response to ACD and additional analyses

## 26th January 2023

---


| | |
|---|---|
| **Produced by** | Peninsula Technology Assessment Group (PenTAG)<br>University of Exeter Medical School<br>South Cloisters<br>St Luke's Campus<br>Heavitree Road<br>Exeter<br>EX1 2LU |
| **Authors** | **Madhusubramanian Muthukumar**[1]<br>**Helen Coelho**[1]<br>**Edward CF Wilson**[1]<br>**Naomi Shaw**[1]<br>**Rebecca Bilden**[1]<br>**G.J. Melendez-Torres**[1]<br>[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter |
| **Correspondence to** | G.J. Melendez-Torres<br>3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; pentag@exeter.ac.uk |

**Produced by**

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

**Date completed** 26/01/2023

**Source of funding** This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135524.

**Declared competing interests of the authors** None

**Acknowledgments** The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG), and clinical advice provided by Dr David Halpin (Royal Devon University Healthcare NHS Trust)

**Rider on responsibility for document** The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows** Muthukumar M, Coelho H, Wilson ECF, Shaw N, Bilden R, Crathorne L, Melendez-Torres GJ. Tezepelumab for treating severe asthma [ID3910] A Single Technology Appraisal. Addendum #1: EAG review of Company's Response to ACD and additional analyses Peninsula Technology Assessment Group (PenTAG), 2022.

## Table of Contents

## List of tables

## Abbreviations

| Acronym | Definition |
|---|---|
| AAER | Annualised asthma exacerbation rate |
| ACQ-6 | Asthma Control Questionnaire 6-item |
| AE | Adverse event |
| AER | Asthma exacerbation rate |
| AERR | Asthma exacerbation rate reduction |
| AI | Adrenal insufficiency |
| AQLQ | Asthma Quality of Life Questionnaire |
| AQLQ(S)+12 | Asthma Quality of Life Questionnaire (Standardised) for 12 years and older |
| ASD | Asthma Symptom Diary |
| BD | Bronchodilator |
| BMI | Body mass index |
| BTS | British Thoracic Society |
| CEAC | Cost-effectiveness acceptability curve |
| CFB | Change from baseline |
| CGI-C | Clinician Global Impression of Change |
| CI | Confidence interval |
| Con Ex | Controlled exacerbations |
| CRD | Centre for Reviews and Dissemination |
| CS | Company Submission |
| CSE | Clinically significant exacerbations |
| CSR | Clinical study report |
| DASD | Daily Asthma Symptom Diary |
| EAG | External Assessment Group |
| ED | Emergency department |
| EOS | Eosinophil |
| EQ-5D | European Quality of Life-5 Dimensions |
| EQ-5D-3L/5L | European Quality of Life-5 Dimensions-3 Levels/5 Levels |
| EU | Europe |
| FAD | Final appraisal document |
| FAS | Full analysis set |
| $FEF_{25–75\%}$ | Forced expiratory flow over 25–75% of the vital capacity |
| $FEV_1$ | Forced expiratory volume in the first second |
| FEIA | Fluorescent enzyme immunoassay |
| FeNO | Fractional exhaled nitric oxide |

| Acronym | Definition |
|---|---|
| FVC | Forced vital capacity |
| GEE | Generalized estimating equation |
| GINA | Global Initiative for Asthma |
| HR | Hazard ratio |
| HSE | Health Survey for England |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| ICS | Inhaled corticosteroids |
| IgE | Immunoglobulin E |
| IL | Interleukin |
| IPD | Individual patient-level data |
| ITT | Intent-to-treat |
| IU | International Unit |
| IV | intravenous |
| LABA | Long-acting beta agonist |
| LAMA | Long-acting muscarinic antagonist |
| LOCF | Last observation carried forward |
| LS | Least squares |
| LY | Life years |
| MMRM | Mixed-effects model for repeated measures |
| mOCS | Maintenance oral corticosteroid treatment |
| NA | Not applicable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMA | Network meta-analysis |
| NR | Not reported |
| OCS | Oral corticosteroid |
| ONS | Office for National Statistics |
| OR | Odds ratio |
| OWSA | One-way sensitivity analysis |
| PAS | Patient Access Scheme |
| PBO | Placebo |
| PEF | Peak expiratory flow |
| PGI-C | Patient Global Impression of Change |
| PGI-I | Patient Global Impression of Improvement |
| PGI-S | Patient Global Impression of Severity |
| PSS | Personal Social Services |

| Acronym | Definition |
|---|---|
| Q2W | Once every two weeks |
| Q4W | Once every four weeks |
| QA | Quality assessment |
| QALY | Quality-adjusted life year |
| QC | Quality check |
| RCT | Randomised controlled trial |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SCS | Systemic corticosteroid |
| SE | Standard error |
| SF-12/36 | 12-Item/36-Item Short Form Health Survey |
| SGRQ | St George's Respiratory Questionnaire |
| SLR | Systematic literature review |
| SOC | Standard of care |
| TA | Technology appraisal |
| TAG | Technology appraisal group |
| TEZ | Tezepelumab |
| TP | Transition probability |
| UK | United Kingdom |
| UK SAR | UK Severe Asthma Registry |
| Uncon Ex | Uncontrolled exacerbations |
| VAS | Visual analogue scale |

# 1. INTRODUCTION

In response to NICE's Appraisal Consultation Document (ACD, November 2022) following the first Appraisal Committee meeting for tezepelumab for treating severe asthma, the company submitted a response with a revised base case analysis. This report summarises the EAG's critique of that response.

# 2. EAG RESPONSE

## 2.1. Definition of treatment response

The company's decision model focuses on asthma control and exacerbations as the key drivers of costs and outcomes, the probabilities of which are determined by treatment. However, the model also includes a response assessment at 52 weeks. Those deemed 'non-responders' discontinue treatment (receiving SoC) whilst responders continue. In its initial submission the company defined treatment response as any reduction in exacerbations or mOCS dose (CS sect B3.2.2.3). The EAG notes that the committee considered this to be inappropriate, requesting that a ≥50% reduction in both exacerbations and mOCS dose should be used (ACD sect 3.6 and 3.18).

The company's revised base case does not match this recommendation, instead defining response as:

- For patients not on maintenance oral corticosteroids (mOCS): ≥50% reduction in exacerbations
- For patients on mOCS: ≥50% reduction in mOCS dose

That is, there is no requirement for a reduction in exacerbations *as well* as a reduction in dose for those patients on mOCS.

This was following clinical expert advice to the company that "[m]OCS reduction is the key outcome for these patients, regardless of exacerbation reduction." (Company response p3) This comment was driven by the desire to reduce the risks of long-term OCS use. Furthermore, the company feels that the 'AND' criterion (reductions in mOCS AND exacerbations) is inconsistent with previous appraisals (which have employed an 'OR' criterion: reductions in either) and sets a higher bar for tezepelumab than for other biologics. The company also notes that there is a high positive correlation between mOCS dose and exacerbations (reductions in one imply a reduction in the other), although the EAG notes the company reports that whilst 55 (74% of 74) patients treated with tezepelumab achieved ≥50% reduction in mOCS dose in the SOURCE trial, [redacted] achieved both mOCS dose reduction AND ≥50% reduction in exacerbations, implying less than perfect correlation (company response p4).

The company provides three options in its revised model: its original base case (any reduction in exacerbations or mOCS dose), its revised base case (reduction in in exacerbations for patients not on mOCS and reduction in dose for those on mOCS), and the committee's preferred scenario (reduction in exacerbations AND mOCS dose for those on mOCS).

The EAG notes differences in transition probabilities reported by the company in its response. These show a more favourable set of probabilities for the tezepelumab arm compared with the company's original base case post response assessment (Company response Tables 9-18). This is as expected as the stricter definition of response means a greater proportion of patients should fail to respond (i.e. discontinuation rates should be higher). The transition probabilities are then recalculated for the remaining pool of patients defined as responders.

However, the EAG notes that in the company's preferred scenario, discontinuation rates for patients taking tezepelumab in most of the subgroups in the mOCS population are substantially lower than the previous base case (Company response Table 19), which the EAG feels lacks face validity. (The exception is in the non-bio eligible subgroup where the discontinuation rate is substantially higher).

Whilst the EAG acknowledges the company's concerns with the strict definition of response preferred by the committee, on balance the EAG's preference is to align with the committee's preferred definitions.

## 2.2. Efficacy of tezepelumab vs placebo

No new data or analyses were presented by the company in respect of this issue.

## 2.3. Uncertainty in network meta-analyses

The EAG reiterates that apart from specific views about the choice of subgroups to inform analysis, the uncertainty generated through the network meta-analyses does not arise from substandard conduct of the NMAs, but rather from the challenges of matching exact subgroups to available data from published trials. However, the EAG notes that this uncertainty is not resolved by the analyses or assertions made by the company in the ACD response.

### 2.3.1. Uncertainty in network meta-analyses generally

In response to concerns about uncertainty in the network meta-analyses (NMAs), the company advances three main points, specifically the company a) presents additional analyses, b)

compares findings to another published NMA, and c) asserts that any differences in length of follow-up time are likely biased against tezepelumab.

Additional analyses presented by the company include a simulated treatment comparison. As noted by the EAG in the original report, these analyses rely on a 'one-by-one' comparison strategy and thus are not suitable for an EAG base case. Moreover, the simulated treatment comparison is not suitable for verifying NMA results given that each comparison will contain a different distribution of effect modifiers.

Comparisons to another published NMA are useful but not dispositive. This is because (as noted above) the EAG's concern with the company's provided NMAs was not one of quality but of the inherent difficulties in approximating the exact definition for each population via subgroup NMAs.

Finally, the company notes that differences in follow-up times would likely be biased against tezepelumab on the basis that longer follow-ups would provide the basis for more treatment waning and greater placebo response in AAER and mOCS reduction NMAs respectively. The EAG does not agree that this is obviously the case; for example, while mOCS reduction in the placebo arm may benefit from more attempts at reduction, the same would apply for the tezepelumab arm. The EAG maintains that the uncertainty induced by differing follow-up times is not amenable of categorisation.

### 2.3.2. Relevance of the AAER with hospitalisation

The company notes that having accepted the EAG's base case relating to exacerbation split, criticisms of the use of the NMA for AAER relating to hospitalisation in the economic model are no longer relevant. The EAG agrees with this assertion.

### 2.3.3. Alignment of inputs to anti-IL5 and reslizumab-eligible subgroups

In an effort to make consistent the different subgroups used across antil-IL5 and reslizumab-eligible populations, the company updated their base case to draw on NMAs for AAER and OCS reduction from the high EoS (≥300 cells/μl) subgroup. The EAG agrees that this is a reasonable step and reflects an updated understanding of the relevant guidance.

### 2.3.4. Error in dupilumab network meta-analyses

The EAG notes with concern that the company identified an error in the dupilumab NMAs, but no further information was provided to clarify the impact of this. The EAG maintains that the

most appropriate subgroup for this analysis is EoS ≥150 cells/µl. The EAG's preferred base case therefore reflects this.

## 2.4. Health-related quality of life

### 2.4.1. Utility addition associated with biologic therapy over and above impact on health.

The EAG notes the committee's recommendation to remove this and furthermore the company confirms the original analysis contained an error. The parameter has been removed and the EAG has no further comment to add.

### 2.4.2. Utility estimates for A&E vs mOCS burst

The EAG notes re-estimation of the health state utility regression analysis yields point estimates for the disutility associated with an A&E attendance of [redacted] and [redacted] for an mOCS burst. Whilst the estimates are similar, the point estimates lack face validity as the disutility associated with an asthma episode requiring A&E attendance would be expected to be more severe (higher) than that from one only requiring a burst of oral steroids. The EAG notes that the confidence intervals are wide / the coefficients are not statistically significant. Therefore, the observed point estimates are highly susceptible to (random) sampling error. Whilst the EAG retains the health state utilities provided in the company's revised analysis for its base case, scenario analyses are performed (1) assuming an equal disutility between the two and (2) a reversal of the point estimates.

## 2.5. Mortality

The EAG notes that the committee concluded that the mortality estimates used by the company were appropriate (NICE ACD Section 3.15). Nevertheless, following the appraisal committee meeting, the company provided additional analyses: (1) conducting an analysis of CPRD data for its revised base case, (2) a scenario analysis based on a study set in France reporting all-cause mortality in a cohort with severe uncontrolled asthma,(1) and (3) a further scenario based on the mid-point between the two estimates.

Reviewing the protocol of the company's CPRD analysis, the samples selected appear to match the relevant populations in the various subgroups in the economic model. The EAG notes the sample sizes for most subgroups may provide 'reasonable' bounds of uncertainty with n ranging from [redacted] to [redacted], although notes that larger sample sizes are required to detect differences

in rare events, which may be the case for mortality. The exceptions are for the dupilumab (n = [redacted]) and omalizumab (n = [redacted]) subgroups which yielded very small sample sizes.

Whilst the CPRD study appears well conducted, and that this is an appropriate data source for a NICE appraisal, the EAG has a number of concerns and queries with regards to how the results were incorporated in the model, as well as comparisons of the results with similar CPRD studies.

### 2.5.1. Results are only reported and used from the biologic-ineligible subgroup

Sample sizes are reported for the overall target population of the NICE appraisal (n=[redacted]) and for each subgroup. However, the reported results only pertain to the subset of patients ineligible for a biologic therapy (n=[redacted]). These appear to have been applied across all subgroups in the model. This does not seem the most appropriate approach. It would have been preferable to use the full target population across all subgroups as this would provide more precise estimates due to the larger sample size ([redacted] vs [redacted]). Alternatively, mortality rates by subgroup should be applied to their respective mortality rates individually in the model. The EAG notes that the time period for data extraction from the CPRD was selected specifically to exclude biologic therapy, so there is zero / minimal risk of contamination with the effects of biologic therapies in the CPRD sample thus the EAG has a preference for the larger 'target population of the NICE appraisal' sample to be used.

### 2.5.2. Uncertainty in CPRD estimates is not carried through to multipliers thus underestimating uncertainty in modelled mortality rates

The company's model compares the 10-year mortality rates (by age band) from the CPRD analysis with 10-year mortality rates implied in the company's original model. Model mortality rates are adjusted (calibrated) until they match the CPRD rates, yielding a set of multipliers by age band. Original per-cycle mortality rates are then multiplied by this to increase the death rates predicted by the model to match the CPRD probabilities.

However, due to sampling uncertainty, the multipliers themselves are subject to uncertainty. This uncertainty may be substantial, given the limited sample size of the CPRD study and the relative rarity of mortality events. However, this is not followed through into the decision model. It would have been preferable for the company's probabilistic sensitivity analysis to include a probability distribution around the CPRD death rates by age band, and to sample from this to

recalibrate the multipliers for each simulation. The EAG understands that this would be time-consuming and complex to code, but nevertheless the company's model underestimates uncertainty in mortality estimates.

### 2.5.3. Calibrating *exacerbation-related* mortality to *all-cause* mortality may overestimate modelled mortality

Deaths occurring due to all causes might not necessarily be strictly because of asthma or its exacerbations. The co-morbidities of the patients could have contributed to or caused the death despite the primary admission being for asthma. Watson et al. (2007)(2) showed that though the primary admission might have happened for asthma the death could have been caused by a secondary comorbidity. For instance, the respiratory tract infection which was the most prevalent comorbidity for J45 admissions was found to cause around 17% secondary admissions.

The EAG considered calibrating non-exacerbation related mortality to the same level as all-cause mortality and re-calculate exacerbation related mortality accordingly. However, the model coding merged non-exacerbation mortality with background (i.e., age and gender specific) mortality. Recoding this requires further alterations to Markov calculations which was not possible within the given timeframe.

### 2.5.4. Other similar CPRD studies report lower mortality rates

A recent multinational cohort study of mortality in patients with asthma (Engelkes et al. 2020)(3) which compared UK CPRD data from between 2008-2013 with similar data from four other European countries (NL, DK, ES, IT) suggested a lower all-cause mortality rate in the UK than observed in the company's CPRD analysis. Table 1 compares all-cause mortality rates derived from the company's original model SoC arm, the CPRD-ONS data (company's revised base case post AC1) and the Engelkes study. Engelkes et al.(3) also noted that the cause of death was not reported in a substantial proportion of deaths (as high as 80%) in case of CPRD.

**Table 1 Comparison of mortality rates: company base case, revised base case and Engelkes et al.(3)**

| Age group | All-cause mortality rate* (based on SoC arm of original company model) | All-cause mortality rate* (based on CPRD-ONS data used in the revised company model) | Age group | All-cause mortality rate* (per online Table 2; Engelkes et al. 2020) |
|---|---|---|---|---|
| <50 | 0.7 | 0.0 | 18-<35 yrs. | 1.2 |
| | | | 35-<45 yrs. | 1.8 |
| | | | 45-<55 yrs. | 4.0 |
| 50-<60 | 11.6 | 36.6 | 55-<65 yrs. | 6.7 |
| 60-<70 | 19.5 | 21.8 | 65-<75 yrs. | 14.6 |
| 70-<80 | 35.7 | 67.4 | >=75 yrs. | 54.6 |
| 80-<90 | 90.9 | 186.0 | | |
| 90+ | 260.6 | 477.3 | | |

*expressed as number of deaths per 1000 PY. Note age bands do not align.

### 2.5.5. EAG preferred mortality scenario

The EAG's base case is to default to the committee's preferred mortality estimates (as per the company's original submission).

## 2.6. Company changes to base case

Changes to the company base case in the light of the committee's recommendations are summarised in Table 2 below.

**Table 2 Comparison of committee preferences, company revised base case and EAG revised base case**

| Committee Preferences | Included in company base case | Included in EAG base case |
|---|---|---|
| Treatment response defined as ≥50% reduction in exacerbations AND mOCS dose | ☒ | ☑ |
| Uncertainties in NMA addressed | ☒ | ☑ |
| No additional utility gain for people having biological treatments | ☑ | ☑ |

## 2.7. EAG revised base case

Table 3 to Table 7 show deterministic results for (i) the company's prior base case, (ii) their revised base case post AC1, (iii) the company's revised base case but using the EAG's preferred asthma mortality rates, (iv) the company's revised base case using the EAG's preferred definition of response, and (v) the EAG's preferred base case which comprises (iii) and (iv) together. The final set of rows (vi) shows the probabilistic results for the EAG's preferred base case. Results for the five subgroups are in the five separate tables. Note that in Table 5 (dupilumab eligible subgroup), an additional analysis set is included with the EAG's preferred exacerbation rates based on the NMA subgroup with EoS ≥150 cells/µl. (Additional scenarios exploring the impact of health state utilities are in Section 2.8 below.)

**Table 3: EAG's preferred model assumptions (anti-IL5 eligible)**

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Company prior base-case** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Company revised base-case post AC1** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.6* | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Asthma mortality as per committee preference (based on NICE TA565)** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Committee preferred response definition for people with severe uncontrolled asthma on mOCS** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.1* | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case deterministic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case probabilistic)** | | | | | | |

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |

Fully incremental results presented.

Abbreviations: EAG, External Assessment Group; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

**Table 4: EAG's preferred model assumptions (reslizumab eligible)**

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **EAG corrected company prior base-case** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Company revised base-case post-AC1** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.6* | [redacted] | [redacted] | **-** | **-** | **-** |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Asthma mortality as per committee preference (based on NICE TA565)** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Committee preferred response definition for people with severe uncontrolled asthma on mOCS** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.1* | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case deterministic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case probabilistic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Mepolizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Benralizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| Reslizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |

Fully incremental results presented.

Abbreviations: EAG, External Assessment Group; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

### Table 5: EAG's preferred model assumptions (dupilumab eligible)

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Company prior base-case** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Company revised base-case post AC1** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.6* | [redacted] | [redacted] | - | - | - |
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Asthma mortality as per committee preference (based on NICE TA565)** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | [redacted] | [redacted] | - |
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Committee preferred response definition for people with severe uncontrolled asthma on mOCS** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.1* | Not applicable | | | | |
| Dupilumab + SoC | | | | | | |
| **Relative exacerbation rate for dupilumab based on High EoS >150** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | | | |
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case deterministic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | | | |
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case probabilistic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | | | |
| Dupilumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |

Abbreviations: EAG, External Assessment Group; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

**Table 6: EAG's preferred model assumptions (omalizumab eligible)**

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Company prior base-case** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** - | [redacted] | [redacted] | - | - | - |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Company revised base-case post AC1** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.6* | [redacted] | [redacted] | - | - | - |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Asthma mortality as per committee preference (based on NICE TA565)** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | - | - | - |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Committee preferred response definition for people with severe uncontrolled asthma on mOCS** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | - | - | - |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case deterministic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.1* | [redacted] | [redacted] | | | - |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |
| **Cumulative (EAG preferred base case probabilistic)** | | | | | | |

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | | | |
| Omalizumab + SoC | | [redacted] | [redacted] | [redacted] | [redacted] | Dominated |

Abbreviations: EAG, External Assessment Group; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

**Table 7: EAG's preferred model assumptions (non-bio eligible)**

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Company prior base-case** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | [redacted] | [redacted] | £29,968 |
| SoC | | [redacted] | [redacted] | - | - | - |
| **Company revised base-case post AC1** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.6* | [redacted] | [redacted] | [redacted] | [redacted] | £17,251 |
| SoC | | [redacted] | [redacted] | - | - | - |
| **Asthma mortality as per committee preference (based on NICE TA565)** | | | | | | |
| Tezepelumab (PAS price) + SoC | ***Error! Reference source not found.*** | [redacted] | [redacted] | [redacted] | [redacted] | £34,458 |
| SoC | | [redacted] | [redacted] | - | - | - |
| **Committee preferred response definition for people with severe uncontrolled asthma on mOCS** | | | | | | |
| Tezepelumab (PAS price) + SoC | *2.1* | [redacted] | [redacted] | [redacted] | [redacted] | £19,428 |
| SoC | | [redacted] | [redacted] | - | - | - |

| Preferred assumption | Section in EAG response | Total costs | Total QALYs | Incremental cost | Incremental QALYs | ICER £/QALY |
|---|---|---|---|---|---|---|
| **Cumulative (EAG preferred base case deterministic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | [redacted] | [redacted] | £31,608 |
| SoC | | [redacted] | [redacted] | - | - | - |
| **Cumulative (EAG preferred base case probabilistic)** | | | | | | |
| Tezepelumab (PAS price) + SoC | - | [redacted] | [redacted] | [redacted] | [redacted] | £32,019 |
| SoC | | [redacted] | [redacted] | - | - | - |

Abbreviations: EAG, External Assessment Group; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

## 2.8. EAG scenarios (post AC1)

Table 8 below presents the results of additional utility scenarios conducted by EAG following company's revised base case with 'no biologic specific utility' post AC1. Results are almost completely insensitive to the assumed scenarios.

**Table 8. EAG scenarios following company's revised model post AC1**

| Preferred assumption | Section in EAG ACD response | Incremental costs | Incremental QALYs | ICER £/QALY (tezepelumab+ SoC vs. comparator) | +/- company base case* |
|---|---|---|---|---|---|
| ***Anti-IL5 eligible^ (Comparators: Mepolizumab+SoC, Benralizumab+SoC)*** | | | | | |
| Company's revised base case post AC1 | *2.6* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | - |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | |
| A&E utility same as mOCS burst | *2.4.2* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| A&E and mOCS burst utilities - point estimates reversed | *2.4.2* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| ***Reslizumab eligible^ (Comparators: Mepolizumab+SoC, Benralizumab+SoC, Reslizumab+SoC)*** | | | | | |
| Company's revised base case post AC1 | *2.6* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | - |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | |
| Reslizumab + SoC | | [redacted] | [redacted] | Dominated | |

| Preferred assumption | Section in EAG ACD response | Incremental costs | Incremental QALYs | ICER £/QALY (tezepelumab+ SoC vs. comparator) | +/- company base case* |
|---|---|---|---|---|---|
| A&E utility same as mOCS burst | *2.4.2* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Reslizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| A&E and mOCS burst utilities - point estimates reversed | *2.4.2* | | | | |
| Mepolizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Benralizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| Reslizumab + SoC | | [redacted] | [redacted] | Dominated | *0%* |
| ***Dupilumab eligible (Comparator: Dupilumab+SoC)*** | | | | | |
| Company's revised base case | *2.6* | [redacted] | [redacted] | Dominated | - |
| A&E utility same as mOCS burst | *2.4.2* | [redacted] | [redacted] | Dominated | *0%* |
| A&E and mOCS burst utilities - point estimates reversed | *2.4.2* | [redacted] | [redacted] | Dominated | *0%* |
| ***Omalizumab eligible (Comparator: Omalizumab+SoC)*** | | | | | |
| Company's revised base case | *2.6* | [redacted] | [redacted] | Dominated | - |
| A&E utility same as mOCS burst | *2.4.2* | [redacted] | [redacted] | Dominated | *0%* |
| A&E and mOCS burst utilities - point estimates reversed | *2.4.2* | [redacted] | [redacted] | Dominated | *0%* |
| ***Non-bio eligible, 3+ exacerbations or mOCS (Comparator: SoC)*** | | | | | |
| Company's revised base case | *2.6* | [redacted] | [redacted] | £17,251 | - |
| A&E utility same as mOCS burst | *2.4.2* | [redacted] | [redacted] | £17,249 | *0%* |
| A&E and mOCS burst utilities - point estimates reversed | *2.4.2* | [redacted] | [redacted] | £17,258 | *0%* |

## 3. REFERENCES

1. Roche N, Garcia G, de Larrard A, Cancalon C, Bénard S, Perez V, et al. Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective, observational RESONANCE study in France. BMJ Open. 2022;12(8):e060160.

2. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med. 2007;101(8):1659-64.

3. Engelkes M, de Ridder MA, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, et al. Multinational cohort study of mortality in patients with asthma and severe asthma. Respir Med. 2020;165:105919.