NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tezepelumab for treating severe asthma [ID3910]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tezepelumab for treating severe asthma [ID3910]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Astrazeneca Ltd**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. British Society for Allergy & Clinical Immunology (BSACI)
   b. SANOFI
   c. British Thoracic Society
   d. NHS England
   e. Asthma + Lung UK

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Anne Little – Patient Expert, nominated by Asthma +Lung UK

5. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Professional group	British Society for Allergy & Clinical Immunology (BSACI)	Following on from point 1, it is likely that anti-alarmin biological therapies for asthma will be most appropriate in the future as prophylactic treatment to prevent airways remodelling and irreversible obstruction in patients identified as being at risk: biomarkers designating such patients, if and when they are defined, will likely comprise the true biomarkers dictating the appropriateness of therapy with biological agents.	Thank you for your comment. Comment noted.
2	Professional group	British Society for Allergy & Clinical Immunology (BSACI)	Key clinical issues (slide 2): NMAs. Since there is no accepted protocol to define the inherent variability of blood eosinophil counts and FeNO within a given individual patient with asthma and how these may vary according to the time of day and the timing of and compliance with prescribed therapy, particularly topical and systemic glucocorticoid, it seems premature to assume that these markers measured on a single occasion are of any clinical significance even if differences between groups of patients can be demonstrated retrospectively in single, cross-sectional meta-analyses.	Thank you for your comment. The committee took these additional analyses into its decision making. The committee considered that the updated NMAs provided reassurance and was satisfied that the company had explored the uncertainty in its updated NMAs and that there were unresolvable challenges in matching exact subgroup data because of the lack of evidence. The committee concluded that tezepelumab is likely to have a similar clinical effectiveness compared with existing biological treatments, but this was highly uncertain. (See section 3.10 of the FAD).
3	Professional group	British Society for Allergy & Clinical Immunology (BSACI)	Slide 7. There is arguably no such thing as “Allergic IgE mediated asthma”. Type 1 hypersensitivity to inhaled aeroallergens may exacerbate asthma symptoms in patients who are clinically sensitised, but this is a minor contribution to symptomatology as demonstrated by the lack of therapeutic effect of anti-histamines. Omalizumab likely reduces the rate of exacerbation of asthma principally by restoring innate immunity to respiratory tract viral infection (discussed in Riccardi D et al. Eur Resp J 2022 Aug 10; 60(2):2102103. doi: 10.1183/13993003.02103-2021).	Thank you for your comment. Comment noted.
4	Professional group	British Society for Allergy & Clinical Immunology (BSACI)	Key clinical issues (slide 2): Correct inhaler technique, as well as perfect compliance when delivering topical therapy to the airways of asthmatics may have profound effects on symptomatology and “exacerbation” of asthma (see Dekhuijzen PNR et al. J Allergy Clin Immunol Pract 2022 Jul;10(7):1813-1824.e1. doi: 10.1016/j.jaip.2022.03.013) and is considered in none of the studies included in this analysis. Groups of patients randomised to receiving, or not receiving regular, effective tuition in using suitable inhaler devices and encouragement to comply as requested with therapy should ideally be included as additional “placebo” groups in trials of the possible effects of biological therapies if their true worth in relationship to “conventional” therapies is to be evaluated, otherwise the	Thank you for your comment. Comment noted.

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			contribution of these factors to poor asthma control, which may be considerable, cannot be evaluated.	
5	Professional group	British Society for Allergy & Clinical Immunology (BSACI)	As remarked already in slide 8 (for example), an acceptable treatment "response", in terms of symptomatology, symptom frequency and period of observation (and in addition to having eliminated poor inhaler technique and/or compliance as possible contributors) remains to be defined.	Thank you for your comment. Comment noted.
6	Patient expert	NA	Although I am not a numbers person, I can grasp the rationale for needing a clear definition of 'controlled' severe asthma in order to measure/analyse treatment outcomes and keep trials on a certain trajectory. However, **I just wonder if there is a risk of definitions becoming rigid to the point where patients who might benefit, lose out**?	Thank you for your comment. Comment noted.
7	Patient expert	NA	Expanding on 2… **is there scope for a little more qualitative data from patients on what is meant by a 'meaningful reduction in exacerbations'**?	Thank you for your comment. Comment noted.
8	Patient expert	NA	**What really strikes me about Tezepelumab is that it targets the top of the inflammatory cascade. If this is the case, could the drug have long term health benefits for all severe asthmatics beyond those offered by other biologics?** I am not an expert by any means, but if Tezepelumab intervenes at the top of the inflammatory cascade does this mean it has the potential to stick a spanner in the works before airway re-modelling processes leading to long term damage become established?	Thank you for your comment. Comment noted.
9	Patient expert	NA	Expanding on 4… **could Tezepelumab be a more cost efficient treatment for severe asthma than other biologics?**	Thank you for your comment. Comment noted.
10	Comparator company	SANOFI	On paragraph 3.4 the proposed population for tezepelumab includes those who are having maintenance oral corticosteroids. In the SOURCE study, however, tezepelumab did not meet its primary endpoint of a categorised percentage reduction in final daily oral corticosteroid dose at week 48 versus placebo. Also, the odds of achieving a category of greater percentage reduction in daily maintenance oral corticosteroid dose at week 48 were higher, but not significantly in the tezepelumab group than in the placebo group in patients with a baseline blood eosinophil count of at least 150 cells per µL, which is consistent with a previous oral corticosteroid-sparing study of an asthma biologic. Given the available evidence, we believe additional data for severe asthma patients who are dependent on maintenance oral corticosteroids is required to ensure that tezepelumab is an appropriate intervention for this cohort.	Thank you for your comment. Comment noted.
11	Patient/carer group	British Thoracic Society	We agree with the clinical and patient experts that there is an unmet need for treatments that reduce exacerbations and thereby also reduce steroid related side effects. Tezepelumab is novel in its mechanism of action and therefore can be beneficial for patients who do not fulfil prescribing criteria for existing biologic treatments. We agree with the clinical expert that this is likely to be ~5% of people. The committee have commented that Tezepelumab has not been compared	Thanks for your comment. The committee took unmet need into consideration along with the company's updated modelling and the updated discount. The recommendation has changed and Tezepelumab is recommended for treating severe asthma in people 12 years and over, when treatment with high-dose inhaled

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			directly with other biological treatments- however as its mechanism of action and target population will be different, this comparison, while clinically helpful, should not be prioritised within the consultation.	corticosteroids plus another maintenance treatment has not worked well enough. It is recommended only if: • people have had 3 or more exacerbations in the previous year or are having maintenance oral corticosteroids. (See section 3.22 of the FAD)
12	Patient/carer group	British Thoracic Society	3.6 Treatment response We feel that treatment response should be defined as a 50% reduction in exacerbation frequency OR a 50% reduction in maintenance oral corticosteroid dose within the first 12 months. This is the criteria by which response to other biologics are assessed. We agree that the company's definition of treatment response was not appropriate.	Thank you for your comment. The committee took this information and additional justification provided by the company and clinical experts opinion into its decision making. The committee concluded that the company's updated definition of treatment response was appropriate for decision making. (See section 3.6 of the FAD)
)13	Patient/carer group	British Thoracic Society	3.12 We agree with using an ACQ-6 score of 1.5 as a cur-off to define asthma control status with ACQ-6 score >1.5 indicating uncontrolled asthma	Thank you for your comment. Comment noted.
14	Patient/carer group	British Thoracic Society	3.15 Mortality estimate Mortality related to (severe) asthma is likely to be underestimated as it is much more likely to be related to side effects from long-term and cumulative use or oral corticosteroids, which would not be collected through Health Survey and Registry data, than to acute exacerbations of asthma.	Thank you for your comment. The committee took these comments into consideration along with the company's updated mortality in its decision making. The committee consider cost-effectiveness scenarios using both the company's original base-case asthma-related mortality estimates and the all-cause mortality CPRD data (only in the non-biological eligible subgroup) in its decision making. (See section 3.15 of the FAD)
15	Patient/carer group	British Thoracic Society	3.16 Assuming utility gain We disagree with the committee. There is a statistically significant difference in EQ-5D-5L and therefore this should not be ignored.	Thank you for your comment. Comment noted.
16	Patient/carer group	British Thoracic Society	3.18 Further analyses needed: Treatment response should be defined as 50% reduction in exacerbations OR systemic corticosteroid dose and not 'AND'. This is in line with currently licenced biologics (mepolizumab and benralizumab), reflects clinical practice across UK severe asthma centres and the severe asthma toolkit (co-developed by NHS England)	Thank you for your comment. The committee took this information, justification provided by the company and clinical experts opinion into its decision making. The committee concluded that the company's updated definition of treatment response was appropriate for decision making. (see section 3.6)
17	Professional group	NHS England Specialised Commissioning	We agree with the clinical and patient experts that there is an unmet need for treatments that reduce exacerbations and thereby also reduce steroid related side effects. Tezepelumab is novel in its mechanism of action and therefore can be beneficial for patients who do not fulfil prescribing criteria for existing biologic treatments. We agree with the clinical expert that this is likely to be ~5% of people. The committee have commented that Tezepelumab has not been compared directly with other biological treatments- however as its mechanism of action and target population will be different, this comparison, while clinically helpful, should not be prioritised within the consultation.	Thanks for your comment. The committee took unmet need into consideration along with the company's updated modelling and the updated discount. The recommendation has changed and tezepelumab is recommended for treating severe asthma in people 12 years and over, when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough. It is recommended only if: • people have had 3 or more exacerbations in the previous year or are having maintenance oral

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				corticosteroids. (See section 3.22 of the FAD)
18	Professional group	NHS England Specialised Commissioning	3.6 Treatment response We feel that treatment response should be defined as a 50% reduction in exacerbation frequency OR a 50% reduction in maintenance prednisolone dose within the first 12 months. This is the criteria by which response to other biologics are assessed. We agree that the company's definition of treatment response was not appropriate.	Thank you for your comment. The committee took this information, justification provided by the company and clinical experts opinion into its decision making. The committee concluded that the company's updated definition of treatment response was appropriate for decision making. (See section 3.6 of the FAD)
19	Professional group	NHS England Specialised Commissioning	3.12 We agree with using an ACQ-6 score of 1.5 as a cut-off to define asthma control status with ACQ-6 score >1.5 indicating uncontrolled asthma	Thank you for your comment. Comment noted.
20	Professional group	NHS England Specialised Commissioning	3.15 Mortality estimate Mortality related to (severe) asthma is likely to be underestimated as it is much more likely to be related to side effects from long-term and cumulative use or oral corticosteroids, which would not be collected through Health Survey and Registry data, than to acute exacerbations of asthma.	Thank you for your comment. The committee took these comments into consideration along with the company's updated mortality in its decision making. The committee consider cost-effectiveness scenarios using both the company's original base-case asthma-related mortality estimates and the all-cause mortality CPRD data (only in the non-biological eligible subgroup) in its decision making. (See section 3.15 of the FAD).
21	Professional group	NHS England Specialised Commissioning	3.16 Assuming utility gain We disagree with the committee. There is a statistically significant difference in EQ-5D-5L and therefore this should not be ignored.	Thank you for your comment. Comment noted.
22	Professional group	NHS England Specialised Commissioning	3.18 Further analyses needed: Treatment response should be defined as 50% reduction in exacerbations OR oral corticosteroid dose and not 'AND'. This is in line with currently licenced biologics (mepolizumab and benralizumab), reflects clinical practice across UK severe asthma centres and the severe asthma toolkit (co-developed by NHS England)	Thank you for your comment. The committee took these comments into consideration along with the company's updated mortality in its decision making. The committee consider cost-effectiveness scenarios using both the company's original base-case asthma-related mortality estimates and all-cause mortality CPRD data (only in the non-biological eligible subgroup) in its decision making. (See 3.15 of the FAD).
23	Patient/carer group	Asthma + Lung UK	Previous appraisals have taken into account the additional utility gain of biological treatments for people with severe asthma, which in our view is significant. This committee has decided not to take this additional utility gain into account for Tezepelumab, and we disagree with this approach. Severe asthma is often debilitating and severely impacts quality of life, mental health and wellbeing. We know that it results in people feeling isolated, lonely, anxious and fearful, and that it impede their ability to do activities like going to work or participating in physical activity. People with severe asthma have told us	Thank you for your comment. suggested that the regression coefficient was no longer statistically significant for biological-specific utility, so it removed the additional utility gain for biological treatments in its updated base case. The committee agreed that the company's updated base case was appropriate.

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			that: *"Trying to hold down my job and live my life as normally as possible is nearly impossible. Before I was diagnosed with severe asthma, I was an active, happy person who enjoyed the outdoors, spending time with my dog and my horse, and seeing my friends regularly. Now I'm clinging on to my part-time job and am too scared to leave the house in case I have an asthma attack. I live with my mum and on my bad days she is basically my carer..."* *(Fighting Back Report, pg.16)* *"… I spent all the time in hospital. The first few times you get admitted, everybody comes to see you. But then, it gets a little bit boring and out of the way. So, friendships drift off and fall into a bit of isolation, really."* *(Do No Harm Report, pg.14),* It is clear that biologic treatments can have a dramatic and transformative impact and significantly change the quality of life for many of those who receive them. In our 2021 *'Do No Harm'* severe asthma report, we found that: • 43% of respondents with severe asthma said that a biologic had improved their quality of life • 23% said that it's been completely life-changing • 13% also revealed that they are less anxious/scared as a result of a biologic treatment. In our most recent *'Fighting Back'* report we also hear about the wider benefits that people with severe asthma have experienced because of biologic treatments – one supporter told us: *"Biologic drugs have given me my life back. I noticed a huge improvement almost immediately and haven't needed to take steroids since. I can now exercise and have regained my independence and social life..."* Similarly, we conducted six interviews of people with severe asthma in England in our *Falling into Isolation Report*. Participants stated that: *"I just wish I had been put on this biologic a lot sooner. Because the period I was suffering, you can't explain it in words. It was really, really hard for me. It was just so depressing that sometimes you think your life is just not worth living anymore." Participant 1* *"What [the biologic] has also done is give me a sense of confidence…It has just*	

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			provided that extra dimension of freedom, a psychological freedom, really. That's an invaluable thing. It's a really basic thing, not being sick all the time". *Participant 3* *"Well, I actually have a life now, because before I was on a mobility scooter. I was unable to do anything. I wasn't able to leave the house without the scooter. I just had no life. So, yes, it's come back now".* *Participant 5* It is clear that the introduction of biologics can be truly transformational for people with severe asthma. However, not everyone is currently able to benefit from biologic drugs based on clinical biomarkers (FeNO, Blood eosinophils & IgE levels). Tezepelumab however, could change this and has demonstrated improvement in patient outcomes in a broad population of severe asthma patients regardless of clinical biomarker levels. There is a large unmet need in the UK amongst patients that do not meet the eligibility criteria for available biologics. This group carries a significant overall burden of disease, with frequent exacerbations and poor quality of life, yet are unable to receive current biologics. The patient population in question sits at step 5 on the BTS/SIGN guidelines, and therefore are the most severe population of asthma patients. They have the highest disease burden, especially as they must have had 3 or more exacerbations or be on maintenance oral steroids to be eligible for treatment and this population is at a much greater risk of future asthma attacks, hospital visits and therefore possible death. We view Tezepelumab as an big opportunity to improve patient outcomes within this population, and regard the additional utility gain within this group as a significant and important part of Tezepelumab's impact. Given the severity of symptoms experienced by this group, the potential utility gain is significant, and we believe that it should be taken into account fully.	
24	Company	AstraZeneca UK	AstraZeneca welcomes the opportunity to comment on this ACD and will address the issues raised in turn: **1. Definition of treatment response** The company has updated the definition of treatment response in its base-case analysis, to become: • Patients not on maintenance oral corticosteroids (mOCS): ≥50%	Thank you for your comment**.** The committee took this information provided by the company and clinical experts opinion into its decision making**.** The committee concluded that the company's updated definition of treatment response was appropriate for decision making**.** (See section 3.6 of the FAD)

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			reduction in exacerbations • Patients on mOCS: ≥50% reduction in mOCS dose The ACD for tezepelumab for the treatment of severe asthma states that the company's definition of treatment response (any reduction in exacerbations or maintenance oral corticosteroids dose from baseline) is not appropriate. This was based on the EAG considering the definition used as not clinically meaningful which was supported by the clinical expert. Technical discussions with the EAG in advance of the committee meeting and discussions during the committee meeting itself focussed only on the exacerbation reduction component of response. AstraZeneca acknowledges that within the ACD document the committee has requested the use of ≥50% reduction in exacerbations **and** oral corticosteroids dose to be applied in the model, however: a. For patients on mOCS, it is not clear whether it is the intent of the committee that both aspects should apply or whether only the reduction in mOCS dose should apply b. Irrespective of a., the basis for the committee's request in mOCS patients is unclear, as this was not discussed with the clinical expert during the committee meeting (part A at least) In light of this, upon receipt of the ACD, the company sought clinical opinion from Severe Asthma Specialists to determine the appropriate definition of response for patients on mOCS (only these patients, since it is clear that ≥50% reduction in exacerbations is the appropriate definition for patients not on mOCS). Six Severe Asthma Specialists were approached, all of whom stated the appropriate definition to be ≥50% reduction in mOCS dose. Associated comments were that OCS reduction is the key outcome for these patients, regardless of exacerbation reduction. Use of mOCS is associated with long term side effects such osteoporosis, diabetes and cataracts and it is important to reduce the risk of these complications by reducing mOCS dose. The primary endpoint of studies in mOCS patients tends to relate to reduction in mOCS dose. Two specialists stated that ideally total OCS exposure (considering both mOCS use and OCS bursts to resolve exacerbations) should be reduced by ≥50% but the latter is difficult to track. Therefore, in clinical practice, a ≥50% reduction in mOCS dose is the more feasible and practical approach. Accordingly, the company has updated its base case analysis, with treatment	

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			response defined as: • Patients not on mOCS: ≥50% reduction in exacerbations • Patients on mOCS: ≥50% reduction in mOCS dose Model inputs and results of the revised base case and scenario analyses are reported later in this ACD response. <u>A scenario analysis is provided based on our interpretation of the committee's request:</u> • <u>Patients not on mOCS: ≥50% reduction in exacerbations</u> • <u>Patients on mOCS: ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations</u> This scenario reflects our interpretation of the committee's request within the ACD, for patients on mOCS. Model inputs and results of the revised base case and scenario analyses can be found later in this response. <u>For patients on mOCS, ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations, is not an appropriate definition of response</u> The company feels this is not an appropriate definition of response in mOCS treated patients and therefore not suitable for decision-making, because: • This definition appears to be inconsistent with clinical practice - none of the six Severe Asthma Specialists who provided clinical opinion to the company stated this to be the definition of response they employ in clinical practice • The definition is inconsistent with that of previous appraisals of severe asthma biologics for which patients on mOCS are included in the recommendation [1-3]. NICE's recommendations for mepolizumab, benralizumab and reslizumab define an adequate response as a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids **<u>or</u>** a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. There is no clinical rationale as to why response to tezepelumab response should be assessed differently to that of	

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			these other biologics. Furthermore, use of this definition for tezepelumab would create unnecessary variation in care within the NHS and would complicate treatment protocols for severe uncontrolled asthma. • mOCS therapy itself supresses exacerbations quite effectively, meaning this definition sets a very 'high bar'. To accompany the need for a ≥50% reduction in mOCS dose with the need to also reduce exacerbations by ≥50% (over and above the exacerbation reduction attributable to the baseline mOCS dose) sets a very high bar for tezepelumab response. Analysis of SOURCE shows that of the 74 patients treated with tezepelumab, 55 (74%) achieved ≥50% reduction in mOCS dose, whilst [redacted] achieved ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations at week 48. [redacted] • An extension of the above point is that it would also render the economic comparison of tezepelumab to other biologics less reliable, to the detriment of tezepelumab. Use of an 'AND' criteria in mOCS treated patients for tezepelumab would create a difference between how response is assessed for tezepelumab vs. other biologics currently recommended by NICE. In the model, there is no way to differentiate clinical data for other biologics vs. tezepelumab on the basis of differing response definition. This would have the effect of penalising tezepelumab in the economic comparison, as the inherent assumption would be that only 'super responders' to other biologics continue treatment post response assessment, when in fact some lesser responders also continue treatment in clinical practice, given their response criteria. <u>The wording of the recommendation regarding adequate response should mirror that of other biologics whose recommended populations include patients treated with mOCS.</u> Commentary to this point in this ACD response considers the appropriate definition of response to inform numerical analysis in the cost-effectiveness model. The company believes that the wording used in the recommendation should mirror that of other biologics whose recommended populations include patients treated with mOCS, and therefore should include the following wording:	

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			"At 12 months: *stop tezepelumab if the asthma has not responded adequately or* *continue tezepelumab if the asthma has responded adequately and assess response each year.* *An adequate response is defined as:* *a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or* *a clinically significant reduction in continuous oral-corticosteroid use while maintaining or improving asthma control."* The rationale for this being: • **Clinical leeway to consider the totality of response**: Use of the terms "a clinical meaningful/significant reduction", as opposed to quoting specific numerical thresholds, allows clinicians some leeway to consider the totality of response beyond exacerbations and mOCS dose, inclusive of other clinical factors such as ACQ response, FEV1 response and how the patient considers they have responded. For example, consider a patient with a high disease burden who is not on mOCS who had 5 exacerbations in the year prior to biologic treatment. If following a year of biologic treatment this patient had shown a good ACQ and FEV1 response and reports feeling much better but had experienced 3 exacerbations resolved without the need for an A&E visit or inpatient hospitalisation, then against this backdrop the treating clinician is likely to regard this as representing a clinically meaningful reduction in exacerbations. Under a recommendation where a threshold of ≥50% reduction in exacerbations were specified, the clinician would have to stop treatment and switch the patient to an alternative biologic, whereas, under a recommendation which stated a clinically meaningful reduction is needed, the clinician would be able to continue treatment with that same biologic. The company feels this would not create a disconnect between economic modelling and recommendation wording because there would be occasions when the reverse is true, i.e. a ≥50% reduction in exacerbations would not be deemed clinically meaningful because of inadequate response in other areas. Therefore, the ≥50% reduction applied in the economic	

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			model can be thought of as the average threshold for response for modelling purposes. • **Consistency vs. other biologics for which patients on mOCS are included in the recommendation**: As mentioned above, the recommendations for mepolizumab, benralizumab and reslizumab define an adequate response as a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. They do not quote specific numerical thresholds as to what constitutes a clinical meaningful/significant reduction. As such it would be unreasonable to create the situation whereby other biologics whose recommended populations include patients treated with mOCS have a degree of clinical leeway in the response assessment but tezepelumab does not. **NOTE**: **comment on terminology – "exacerbations" vs. "severe exacerbations"** Throughout this appraisal the company has used the term "exacerbations" to align with the terminology used in the pivotal trials of tezepelumab. The definition of an exacerbation in the tezepelumab trials was: "*A worsening of asthma symptoms that led to hospitalisation, an emergency department visit that resulted in the use of systemic glucocorticoids for ≥3 consecutive days, or the use of systemic glucocorticoids for ≥3 consecutive days*". This definition is very similar to the ATS/ERS definition of a severe asthma exacerbation as provided below: **ATS/ERS definition of a severe asthma exacerbation [4]**: • Definition of a severe asthma exacerbation for clinical trials should include at least one of the following: a) Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.	

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			b) Hospitalization or ER visit because of asthma requiring systemic corticosteroids. AstraZeneca considers it would be appropriate to use the term "severe exacerbations" in the recommendation wording regarding adequate response to tezepelumab. We believe NICE may have followed this approach of aligning to ATS/ERS definition when forming the equivalent wording within mepolizumab, benralizumab and reslizumab guidance, since the term used to describe the primary endpoint in the pivotal exacerbation reduction trials for these biologics was not "severe exacerbations". However, for clarity it would be useful to make this distinction in the recommendations for tezepelumab.	
25	Company	AstraZeneca UK	**2. Tezepelumab is generally more effective than placebo for severe asthma in pre-planned and post-hoc subgroups** The company notes that the ACD states "*In SOURCE, tezepelumab was more effective than placebo in reducing maintenance oral corticosteroid dose in subgroups with a higher baseline blood eosinophil count (defined as 150 or 300 cells per microlitre and above) at 48 weeks. Largely similar results for AAER reductions were also reported from NAVIGATOR for most post-hoc subgroups at 52 weeks*." but also goes on to state that "*in SOURCE, tezepelumab only reduced AAER in the anti-interleukin-5 eligible subgroup at 48 weeks*" The company would like to remind the committee that SOURCE was designed specifically to assess the efficacy of tezepelumab in reducing patients' maintenance dosage of OCS (this was the trial's primary endpoint). Patients included in the SOURCE trial were different to those included in NAVIGATOR and PATHWAY as the SOURCE population included only severe uncontrolled asthma patients that specifically required regular maintenance OCS (mOCS) treatment. Patients that require mOCS make up a small subset of severe uncontrolled asthma patients and only accounted for ~9% of patients in NAVIGATOR [5] and 6-11% in PATHWAY. Furthermore, exacerbation reductions in SOURCE were assessed whilst clinicians are attempting to reduce patients' maintenance OCS dose. The treatment effect on exacerbations would therefore be expected to differ compared with other trials where the primary focus was exacerbation reduction. The point estimates for exacerbation reduction compared with placebo reported in SOURCE is similar to	Thank you for your comment. Comment noted.

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			results reported for other biologics in their corresponding OCS-sparing studies. [RR 0.69 (SOURCE) vs 0.68 (SIRIUS/mepolizumab [6])]. AstraZeneca requests that the committee consider these key differences when considering SOURCE data.	
26	Company	AstraZeneca UK	**3. Uncertainty in the network meta-analyses (NMAs)** The company recognises there is uncertainty in the NMA but has taken the approach which minimises uncertainty. Alternative approaches to address the NICE request in the ACD were considered but would have only increased uncertainty in the results. All severe asthma biologics are recommended as treatment options by NICE in subsets of their licensed populations, based on the presence of biomarkers and according to exacerbation history. This is because they cannot be deemed clinically- and cost-effective in their full licensed populations. Biomarkers and exacerbation history are known treatment effect modifiers, which impact clinical- and cost-effectiveness. This is reflected in NICE's recommendations of other biologics. Hence, it was important to account for this in the NMA. To achieve this, we performed NMAs at ITT and subgroup level and informed base case cost-effectiveness analysis with the subgroup NMA that most closely aligned with NICE's recommended population for the comparator in question. The alternative approach of using ITT NMA data throughout would be associated with a greater level of uncertainty, as it would not control for treatment effect modifiers nor reflect clinical practice in England and Wales. Whilst it would be possible to use ITT-based NMA data throughout to inform comparisons in the cost-effectiveness model, this would be associated with a greater level of uncertainty than the current approach because such an approach would: • Inherently assume that all populations in the network are comparable and do not differ with respect to characteristics which modify treatment effect. This assumption is not appropriate for biologics for severe uncontrolled asthma because it is known that ITT populations differ with respect to treatment effect modifying characteristics, such as blood eosinophil count, number of exacerbations in the prior year and total immunoglobulin E [7].	Thank you for your comment. The committee took these additional analyses into its decision making. The committee considered that the updated NMAs provided reassurance and was satisfied that the company had explored the uncertainty in its updated NMAs and that there were unresolvable challenges in matching exact subgroup data because of the lack of evidence. The committee concluded that tezepelumab is likely to have a similar clinical effectiveness compared with existing biological treatments, but this was highly uncertain. (See section 3.10 of the FAD)

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			• Not reflect clinical practice in England and Wales – ITT trial populations for biologics are much broader than their NICE recommended populations, meaning relative treatment effects derived in ITT populations are not generalisable to clinical practice <u>A comprehensive exploration of uncertainty associated with the indirect treatment comparison is provided within this response</u> As well as exploring uncertainty via probabilistic sensitivity analysis (PSA) and via the use of alternative subgroup NMA data reflective of the NICE recommended population (and therefore clinical practice) for that comparator, uncertainty is further explored within this response via the inclusion of additional sensitivity analyses based on: • A simulated treatment comparison (STC) – an advantage of this approach being that it controls for treatment effect modifiers. The company regards this as being appropriate to inform scenario analysis but not base case, because for an STC relative treatment effect is derived in the ITT population of the comparator drug, meaning it is not reflective of the NICE recommended population (and therefore clinical practice in England and Wales) for each comparator. • A published NMA from Ando et al [8] – an externally derived NMA that provides comparative effectiveness on AAER according to blood eosinophil count, for tezepelumab versus benralizumab, mepolizumab and dupilumab Further information on each is provided later in this response. <u>The criticism that the hospitalised AAER endpoint is informed by NMA data relating to a different population (ITT) than that of other endpoints (subgroup) is no longer relevant because the exacerbation split has been assumed to be equal across all biologics. This 'bypasses' the NMA for the hospitalised AAER endpoint</u> Given no relevant subgroup data was available to inform the NMA for the	

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			hospitalised AAER endpoint, the company used the ITT-based NMA data in its submission. This was criticised by the EAG, as stated in the ACD: "*The EAG also noted the mismatch between the subpopulations informing the NMA for the outcome of AAER, and the ITT population informing the outcome of AAER-related hospitalisations*". This criticism, however, is unfounded because in the response to technical engagement the company accepted the EAG's approach of setting the exacerbation split to be equal for all biologics. This approach means that the hospitalised AAER NMA is no longer informing the cost-effectiveness model – it has been bypassed. <u>For this response, for each comparator there is consistency across endpoints in NMA populations informing comparisons</u> For base case analysis in the reslizumab eligible population, NMA data for the EoS High: ≥300 cells/µl subgroup has been used to inform all NMA-based comparisons for this response. This, in conjunction with the hospitalised AAER NMA no longer being used in the model, means there is now internal consistency for each comparator in the population which informs NMA data across the endpoints used in the model (AAER and OCS sparing endpoints). Further detail is provided later in this response. <u>Were there any bias in the NMA associated to differing follow-up times, it is highly likely to favour other biologics</u> The ACD states: *"The EAG noted that the trials included in the NMAs had different follow-up times, which could potentially bias the results of the NMAs.*" In cases where there is a material difference in follow-up times of trials that informed the NMA, tezepelumab trials tended to have longer follow-up periods than those of other biologics (e.g. tezepelumab NAVIGATOR – 52 weeks, tezepelumab PATHWAY – 52 weeks, tezepelumab SOURCE – 48 weeks, mepolizumab MENSA – 32 weeks, mepolizumab MUSCA – 24 weeks, mepolizumab SIRIUS – 32 weeks). If there was any associated bias, it is highly likely it would favour other biologics, because: • **AAER**: Any treatment effect waning for other biologics in the extended timeframe corresponding to the follow-up period of the tezepelumab trials, would lead NMA results to improve from a	

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			tezepelumab perspective (where this data able to be captured for other biologics). Furthermore, from the DESTINATION study, it is known that tezepelumab's one year treatment effect on AAER is sustained in full to the end of year two, not only in the ITT population but also for the subgroups that inform the NMAs used in base case cost-effectiveness analysis (EoS high: ≥300 cells/µl, EoS low: <300 cells/µl, allergic). • **mOCS reduction**: The mOCS dose reduction period in tezepelumab's SOURCE study (36 weeks) was considerably longer than that of other studies (e.g. mepolizumab SIRIUS – 16 weeks). Associated to this, patients in SOURCE were permitted multiple attempts to reduce OCS dose (without losing asthma control). This is thought to have contributed to the strong placebo response seen in the trial. In trials of comparators (including SIRIUS), patients were only allowed one attempt to reduce dose. Thus, over a longer timeframe and with multiple attempts to reduce dose (which is more aligned to clinical practice), a stronger placebo response may be observed, meaning the findings of the NMA are likely to be conservative from the perspective of Tezepelumab. <u>The direction of the NMA is consistent with that of other NMAs, both at the ITT population level and for subgroup NMAs that inform base case</u> The company base case economic model comparing tezepelumab with other biologics is informed by an NMA which includes two outcomes of interest, AAER and reduction in mOCS dose. The company searched for publicly available NMAs to compare with the one informing the base case. An externally derived NMA that provides comparative effectiveness on AAER was identified, while no NMA were found for reduction in mOCS dose. Ando K et al.,[8] compared tezepelumab with other biologics and reported results for AAER. The NMA included results for an ITT population as well as some subgroups (NOTE: the subgroup of people with allergic asthma was not included in this publication). Results were reported compared with benralizumab, mepolizumab and dupilumab 300mg (reslizumab and omalizumab were not captured). Although the 300mg dose for dupilumab is not recommended by NICE, this is included in our analysis	

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			as a proxy for the 200mg dose recommended by NICE for severe uncontrolled asthma. The below summary compares the results from Ando K et al., [8] versus the NMA that informs the company base case published in Menzies-Gow et al.,[7] for the outcome of interest. Comparisons are applicable only for the populations and therapies included in both studies. **ITT population:** • Tezepelumab was consistently favourably associated with numerically lower AAERs and ranked first in both NMAs (Ando K et al., and Menzies-Gow et al.,) • Subsequent favourably ranked treatments varied depending on the publication. Menzies-Gow et al., ranked dupilumab 300mg as the second most favourable treatment in reducing AAER (mean vs tezepelumab: 1.19), while Ando K et al., ranked mepolizumab (mean vs Tezepelumab 1.01). **Sub-group populations:** **NMA EoS High (≥300 cells/µl):** This subgroup informs the company base case for the IL-5 eligible population (Note: reslizumab eligible population also includes high EoS as base case, but it is not possible to conduct the comparison between the two NMA studies, as reslizumab is not included in Ando K et al. [8]. • Tezepelumab was favourably associated with numerically lower AAERs, ranking first in both NMAs in this sub-group of people. • Mepolizumab was the second favourable ranked treatment in both publications followed by benralizumab. • Tezepelumab was numerically and statistically significant favourably associated with lower AAER compared with benralizumab in Ando K et al., [8]. **NMA EoS low (<300 cells/µl):** This subgroup informs the company base case for dupilumab eligible population. The below comparison corresponds to dupilumab 300mg dose as a proxy to	

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			dupilumab's 200mg dose. • Tezepelumab was favourably associated with numerically lower AAERs and ranked first in both network meta-analysis studies in this subgroup (Ando K et al.,[8] and Menzies-Gow et al., ,[7]) • Tezepelumab was also favourably associated with numerically lower AAERs in Menzies-Gow et al., compared with dupilumab 200mg in this subgroup. Tezepelumab was consistently associated with a numerically lower AAER compared with other biologics in two NMA studies in the ITT population and at subgroup level that informs the company base case. In some of the subgroup comparisons (e.g., EoS High ≥300 cells/µl) tezepelumab also demonstrated statistically significant improvements versus another comparator, indicating a consistent favourability in the outcome of interest versus other biologics. The company stands by its use of the subgroup NMA for base case as the approach that minimises uncertainty and best reflects treatment practice in England and Wales The company recognises that in the ideal world, comparisons of tezepelumab to other biologics would be made in the populations that precisely correspond to the biologic eligible populations stemming from NICE's recommendations. However, given the multiple criteria that define biologic eligibility and the fact that the company does not have access to individual patient data for competitor trials, it is not possible to for the company to do this. The company has sought to provide the most relevant comparisons possible given data availability by providing base case analysis using the NMA subgroup data that most closely aligns with eligible populations and by providing sensitivity analysis using an alternative subgroup NMA that could also be deemed to represent the population at hand. In doing so, key treatment effect modifiers are accounted for and so are NICE's eligible populations and therefore clinical practice, as best as is possible. Uncertainty has further been explored via the use of an alternative NMA, an alternative approach to indirect comparison and by the PSA which simulates all likely parameter values for treatment effect. However, the company believes the current subgroup NMA approach is associated with the least uncertainty and retains this to inform its base case.	
27	Company	AstraZeneca UK	**4. Utility gain for being on a biologic**	Thank you for your comment. The committee agreed that the company's updated base case was

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			In line with the NICE request to remove the additional utility gain associated with biological treatments, the company has removed this assumption in its updated base case analysis. The utility gain in the model was included on the basis of supportive results from a regression analysis based on the EQ-5D-5L data collected in the tezepelumab clinical trials. When revisiting the mixed regression utilities model to re-run it without the biologic specific co-efficient, our external vendor identified that an error had been made in the original analysis, relating to subject ID variables. When corrected, the analysis no longer yielded a statistically significant coefficient for biologic-specific utility. As such the original analysis should be regarded as errant. We apologise for the confusion and have removed the biologic specific utility from all analyses going forwards.	appropriate. (see section 3.16 of the FAD)
28	Company	AstraZeneca UK	**5. Mortality** The company recalls that the ACD notes "*there may be additional benefits of tezepelumab not captured but this is uncertain*". It also states in section 3.15 that "*The clinical expert noted that asthma mortality might be higher than both the company's and the EAG's estimates in clinical practice. He also explained that sometimes mortality does not only occur because of exacerbations but also long-term use of oral corticosteroids*" The company has conducted a UK real-world study of all-cause mortality in the non-biologic eligible population of this appraisal and uses this to inform its revised base case cost-effectiveness analysis Based on the comments of the clinical expert at the committee meeting for the current appraisal who stated that asthma mortality might be higher than both the company's and the EAG's estimates, the company has conducted a UK real-world evidence (RWE) study of all-cause mortality in the non-biologic eligible population of interest for this appraisal. The results from this UK RWE study further lend support to results from Roche et al [9], a recently published retrospective observational study of a French healthcare database, which shows all-cause mortality for a cohort of severe uncontrolled asthma patients to be substantially higher than that predicted by the cost-effectiveness model. The combined evidence from the two studies, alongside the comments from the clinical expert at the committee meeting, provides strong evidence for a higher mortality estimate than that currently used in the economic modelling. Based on this, AstraZeneca	Thank you for your comment. The committee took the company's updated mortality estimates in its decision making. The committee noted that the company's original base-case asthma-related mortality estimates were more appropriate but that its CPRD analyses was informative for the non-biological eligible group. The committee consider cost-effectiveness scenarios using both the company's original base-case asthma-related mortality estimates and the all-cause mortality CPRD data (only in the non-biological eligible subgroup) in its decision making. (See 3.15 of the FAD)

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			has updated its base case to include revised mortality estimates from the UK RWE study. The non-biologic eligible population was chosen so that mortality in the standard care (without biologic) arm of the cost-effectiveness model could be calibrated to the findings of the study. In doing so this provides a new mortality 'baseline' in the model, from which mortality for all comparators (including biologics) is derived, via exacerbation-related efficacy inputs. Methods relating to the UK RWE study are described in full later in this response. In summary, a retrospective cohort study of electronic health records from Clinical Practice Research Datalink (CPRD) linked datasets was undertaken. Patients with severe uncontrolled asthma who had 3 or more exacerbations in the prior year or who were on mOCS and currently ineligible for biologics based on NICE's recommendations, were identified based on clinical characteristics. This population was followed over the period 2012-2017, to capture records of death within the Office for National Statistics (ONS) Death Registration Data. As biologic use is not well captured in CPRD, this follow up period was chosen to align with the timeframe when there was extremely low usage of biologics in the UK (only omalizumab was available and its uptake was very low), meaning the data can be deemed representative of the population treated with standard care without biologic. The study found all-cause mortality to be considerably higher than that used in the company's cost-effectiveness modelling to date and in keeping with the findings of the Roche et al study. The company plans to develop a manuscript and publish the study.	

NICE National Institute for Health and Care Excellence

Tezepelumab for treating severe asthma [ID3910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 January 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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NICE National Institute for Health and Care Excellence

Tezepelumab for treating severe asthma [ID3910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 January 2023. Please submit via NICE Docs.

Name of commentators completing form:	[redacted]

Comment number	Comments Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1.	Due to the technical nature of this response including tables, and figures, please see the response below.

Dear Appraisal Committee Members,

AstraZeneca welcomes the opportunity to comment on this ACD and will address the issues raised in turn:

1. Definition of treatment response

The company has updated the definition of treatment response in its base-case analysis, to become:

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

The ACD for tezepelumab for the treatment of severe asthma states that the company's definition of treatment response (any reduction in exacerbations or maintenance oral corticosteroids dose from baseline) is not appropriate. This was based on the EAG considering the definition used as not clinically meaningful which was supported by the clinical expert.

Technical discussions with the EAG in advance of the committee meeting and discussions during the committee meeting itself focussed only on the exacerbation reduction component of response. AstraZeneca acknowledges that within the ACD document the committee has requested the use of ≥50% reduction in exacerbations **and** oral corticosteroids dose to be applied in the model, however:

a. For patients on mOCS, it is not clear whether it is the intent of the committee that both aspects should apply or whether only the reduction in mOCS dose should apply
b. Irrespective of a., the basis for the committee's request in mOCS patients is unclear, as this was not discussed with the clinical expert during the committee meeting (part A at least)

In light of this, upon receipt of the ACD, the company sought clinical opinion from Severe Asthma Specialists to determine the appropriate definition of response for patients on mOCS (only these patients, since it is clear that ≥50% reduction in exacerbations is the appropriate definition for patients not on mOCS). Six Severe Asthma Specialists were approached, all of whom stated the appropriate

definition to be ≥50% reduction in mOCS dose. Associated comments were that OCS reduction is the key outcome for these patients, regardless of exacerbation reduction. Use of mOCS is associated with long term side effects such osteoporosis, diabetes and cataracts and it is important to reduce the risk of these complications by reducing mOCS dose. The primary endpoint of studies in mOCS patients tends to relate to reduction in mOCS dose. Two specialists stated that ideally total OCS exposure (considering both mOCS use and OCS bursts to resolve exacerbations) should be reduced by ≥50% but the latter is difficult to track. Therefore, in clinical practice, a ≥50% reduction in mOCS dose is the more feasible and practical approach.

Accordingly, the company has updated its base case analysis, with treatment response defined as:

- Patients not on mOCS: ≥50% reduction in exacerbations
- Patients on mOCS: ≥50% reduction in mOCS dose

Model inputs and results of the revised base case and scenario analyses are reported later in this ACD response.

A scenario analysis is provided based on our interpretation of the committee's request:

- Patients not on mOCS: ≥50% reduction in exacerbations
- Patients on mOCS: ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations

This scenario reflects our interpretation of the committee's request within the ACD, for patients on mOCS. Model inputs and results of the revised base case and scenario analyses can be found later in this response.

For patients on mOCS, ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations, is not an appropriate definition of response

The company feels this is not an appropriate definition of response in mOCS treated patients and therefore not suitable for decision-making, because:

- This definition appears to be inconsistent with clinical practice - none of the six Severe Asthma Specialists who provided clinical opinion to the company stated this to be the definition of response they employ in clinical practice

- The definition is inconsistent with that of previous appraisals of severe asthma biologics for which patients on mOCS are included in the recommendation [1-3]. NICE's recommendations for mepolizumab, benralizumab and reslizumab define an adequate response as a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids **or** a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. There is no clinical rationale as to why response to tezepelumab response should be assessed differently to that of these other biologics. Furthermore, use of this definition for tezepelumab would create unnecessary variation in care within the NHS and would complicate treatment protocols for severe uncontrolled asthma.

- mOCS therapy itself supresses exacerbations quite effectively, meaning this definition sets a very 'high bar'. To accompany the need for a ≥50% reduction in mOCS dose with the need to also reduce exacerbations by ≥50% (over and above the exacerbation reduction attributable to the baseline mOCS dose) sets a very high bar for tezepelumab response. Analysis of SOURCE shows that of the 74 patients treated with tezepelumab, 55 (74%) achieved ≥50% reduction in mOCS dose, whilst [redacted] achieved ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations at week 48.[redacted]

- An extension of the above point is that it would also render the economic comparison of tezepelumab to other biologics less reliable, to the detriment of tezepelumab. Use of an 'AND' criteria in mOCS treated patients for tezepelumab would create a difference between how response is assessed for tezepelumab vs. other biologics currently recommended by NICE. In the model, there is no way to differentiate clinical data for other biologics vs. tezepelumab on the basis of differing response definition. This would have the effect of penalising tezepelumab in the economic comparison, as the inherent assumption would be that only 'super responders' to other biologics continue treatment post response assessment, when in fact some lesser responders also continue treatment in clinical practice, given their response criteria.

<u>The wording of the recommendation regarding adequate response should mirror that of other biologics whose recommended populations include patients treated with mOCS.</u>

Commentary to this point in this ACD response considers the appropriate definition of response to inform numerical analysis in the cost-effectiveness model. The company believes that the wording used in the recommendation should mirror that of other biologics whose recommended populations include patients treated with mOCS, and therefore should include the following wording:

"At 12 months:

stop tezepelumab if the asthma has not responded adequately or

continue tezepelumab if the asthma has responded adequately and assess response each year.

An adequate response is defined as:

a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or

a clinically significant reduction in continuous oral-corticosteroid use while maintaining or improving asthma control."

The rationale for this being:

- **Clinical leeway to consider the totality of response**: Use of the terms "a clinical meaningful/significant reduction", as opposed to quoting specific numerical thresholds, allows clinicians some leeway to consider the totality of response beyond exacerbations and mOCS dose, inclusive of other clinical factors such as ACQ response, FEV1 response and how the patient considers they have responded. For example, consider a patient with a high disease burden who is not on mOCS who had 5 exacerbations in the year prior to biologic treatment. If following a year of biologic treatment this patient had shown a good ACQ and FEV1

response and reports feeling much better but had experienced 3 exacerbations resolved without the need for an A&E visit or inpatient hospitalisation, then against this backdrop the treating clinician is likely to regard this as representing a clinically meaningful reduction in exacerbations. Under a recommendation where a threshold of ≥50% reduction in exacerbations were specified, the clinician would have to stop treatment and switch the patient to an alternative biologic, whereas, under a recommendation which stated a clinically meaningful reduction is needed, the clinician would be able to continue treatment with that same biologic. The company feels this would not create a disconnect between economic modelling and recommendation wording because there would be occasions when the reverse is true, i.e. a ≥50% reduction in exacerbations would not be deemed clinically meaningful because of inadequate response in other areas. Therefore, the ≥50% reduction applied in the economic model can be thought of as the average threshold for response for modelling purposes.

- **Consistency vs. other biologics for which patients on mOCS are included in the recommendation**: As mentioned above, the recommendations for mepolizumab, benralizumab and reslizumab define an adequate response as a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. They do not quote specific numerical thresholds as to what constitutes a clinical meaningful/significant reduction. As such it would be unreasonable to create the situation whereby other biologics whose recommended populations include patients treated with mOCS have a degree of clinical leeway in the response assessment but tezepelumab does not.

NOTE: **comment on terminology – "exacerbations" vs. "severe exacerbations"**

Throughout this appraisal the company has used the term "exacerbations" to align with the terminology used in the pivotal trials of tezepelumab. The definition of an exacerbation in the tezepelumab trials was:

"*A worsening of asthma symptoms that led to hospitalisation, an emergency department visit that resulted in the use of systemic glucocorticoids for ≥3 consecutive days, or the use of systemic glucocorticoids for ≥3 consecutive days*".

This definition is very similar to the ATS/ERS definition of a severe asthma exacerbation as provided below:

ATS/ERS definition of a severe asthma exacerbation [4]:

Definition of a severe asthma exacerbation for clinical trials should include at least one of the following:

a) Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.
b) Hospitalization or ER visit because of asthma requiring systemic corticosteroids.

Tezepelumab for treating severe asthma [ID3910]

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AstraZeneca considers it would be appropriate to use the term “severe exacerbations” in the recommendation wording regarding adequate response to tezepelumab. We believe NICE may have followed this approach of aligning to ATS/ERS definition when forming the equivalent wording within mepolizumab, benralizumab and reslizumab guidance, since the term used to describe the primary endpoint in the pivotal exacerbation reduction trials for these biologics was not “severe exacerbations”. However, for clarity it would be useful to make this distinction in the recommendations for tezepelumab.

2. Tezepelumab is generally more effective than placebo for severe asthma in pre-planned and post-hoc subgroups

The company notes that the ACD states “*In SOURCE, tezepelumab was more effective than placebo in reducing maintenance oral corticosteroid dose in subgroups with a higher baseline blood eosinophil count (defined as 150 or 300 cells per microlitre and above) at 48 weeks. Largely similar results for AAER reductions were also reported from NAVIGATOR for most post-hoc subgroups at 52 weeks*.” but also goes on to state that “*in SOURCE, tezepelumab only reduced AAER in the anti-interleukin-5 eligible subgroup at 48 weeks*”

The company would like to remind the committee that SOURCE was designed specifically to assess the efficacy of tezepelumab in reducing patients’ maintenance dosage of OCS (this was the trial’s primary endpoint).

Patients included in the SOURCE trial were different to those included in NAVIGATOR and PATHWAY as the SOURCE population included only severe uncontrolled asthma patients that specifically required regular maintenance OCS (mOCS) treatment. Patients that require mOCS make up a small subset of severe uncontrolled asthma patients and only accounted for ~9% of patients in NAVIGATOR [5] and 6-11% in PATHWAY.

Furthermore, exacerbation reductions in SOURCE were assessed whilst clinicians are attempting to reduce patients’ maintenance OCS dose. The treatment effect on exacerbations would therefore be expected to differ compared with other trials where the primary focus was exacerbation reduction. The point estimates for exacerbation reduction compared with placebo reported in SOURCE is similar to results reported for other biologics in their corresponding OCS-sparing studies. [RR 0.69 (SOURCE) vs 0.68 (SIRIUS/mepolizumab [6])].

AstraZeneca requests that the committee consider these key differences when considering SOURCE data.

3. Uncertainty in the network meta-analyses (NMAs)

The company recognises there is uncertainty in the NMA but has taken the approach which minimises uncertainty. Alternative approaches to address the NICE request in the ACD were considered but would have only increased uncertainty in the results.

All severe asthma biologics are recommended as treatment options by NICE in subsets of their licensed populations, based on the presence of biomarkers and according to exacerbation history. This is because they cannot be deemed clinically- and cost-effective in their full licensed populations.

Tezepelumab for treating severe asthma [ID3910]

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Biomarkers and exacerbation history are known treatment effect modifiers, which impact clinical- and cost-effectiveness. This is reflected in NICE's recommendations of other biologics. Hence, it was important to account for this in the NMA. To achieve this, we performed NMAs at ITT and subgroup level and informed base case cost-effectiveness analysis with the subgroup NMA that most closely aligned with NICE's recommended population for the comparator in question.

The alternative approach of using ITT NMA data throughout would be associated with a greater level of uncertainty, as it would not control for treatment effect modifiers nor reflect clinical practice in England and Wales.

Whilst it would be possible to use ITT-based NMA data throughout to inform comparisons in the cost-effectiveness model, this would be associated with a greater level of uncertainty than the current approach because such an approach would:

- Inherently assume that all populations in the network are comparable and do not differ with respect to characteristics which modify treatment effect. This assumption is not appropriate for biologics for severe uncontrolled asthma because it is known that ITT populations differ with respect to treatment effect modifying characteristics, such as blood eosinophil count, number of exacerbations in the prior year and total immunoglobulin E [7].

- Not reflect clinical practice in England and Wales – ITT trial populations for biologics are much broader than their NICE recommended populations, meaning relative treatment effects derived in ITT populations are not generalisable to clinical practice

A comprehensive exploration of uncertainty associated with the indirect treatment comparison is provided within this response

As well as exploring uncertainty via probabilistic sensitivity analysis (PSA) and via the use of alternative subgroup NMA data reflective of the NICE recommended population (and therefore clinical practice) for that comparator, uncertainty is further explored within this response via the inclusion of additional sensitivity analyses based on:

- A simulated treatment comparison (STC) – an advantage of this approach being that it controls for treatment effect modifiers. The company regards this as being appropriate to inform scenario analysis but not base case, because for an STC relative treatment effect is derived in the ITT population of the comparator drug, meaning it is not reflective of the NICE recommended population (and therefore clinical practice in England and Wales) for each comparator.

- A published NMA from Ando et al [8] – an externally derived NMA that provides comparative effectiveness on AAER according to blood eosinophil count, for tezepelumab versus benralizumab, mepolizumab and dupilumab

Further information on each is provided later in this response.

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The criticism that the hospitalised AAER endpoint is informed by NMA data relating to a different population (ITT) than that of other endpoints (subgroup) is no longer relevant because the exacerbation split has been assumed to be equal across all biologics. This 'bypasses' the NMA for the hospitalised AAER endpoint

Given no relevant subgroup data was available to inform the NMA for the hospitalised AAER endpoint, the company used the ITT-based NMA data in its submission. This was criticised by the EAG, as stated in the ACD: "*The EAG also noted the mismatch between the subpopulations informing the NMA for the outcome of AAER, and the ITT population informing the outcome of AAER-related hospitalisations*".

This criticism, however, is unfounded because in the response to technical engagement the company accepted the EAG's approach of setting the exacerbation split to be equal for all biologics. This approach means that the hospitalised AAER NMA is no longer informing the cost-effectiveness model – it has been bypassed.

For this response, for each comparator there is consistency across endpoints in NMA populations informing comparisons

For base case analysis in the reslizumab eligible population, NMA data for the EoS High: ≥300 cells/µl subgroup has been used to inform all NMA-based comparisons for this response.

This, in conjunction with the hospitalised AAER NMA no longer being used in the model, means there is now internal consistency for each comparator in the population which informs NMA data across the endpoints used in the model (AAER and OCS sparing endpoints). Further detail is provided later in this response.

Were there any bias in the NMA associated to differing follow-up times, it is highly likely to favour other biologics

The ACD states: *"The EAG noted that the trials included in the NMAs had different follow-up times, which could potentially bias the results of the NMAs.*"

In cases where there is a material difference in follow-up times of trials that informed the NMA, tezepelumab trials tended to have longer follow-up periods than those of other biologics (e.g. tezepelumab NAVIGATOR – 52 weeks, tezepelumab PATHWAY – 52 weeks, tezepelumab SOURCE – 48 weeks, mepolizumab MENSA – 32 weeks, mepolizumab MUSCA – 24 weeks, mepolizumab SIRIUS – 32 weeks). If there was any associated bias, it is highly likely it would favour other biologics, because:

- **AAER**: Any treatment effect waning for other biologics in the extended timeframe corresponding to the follow-up period of the tezepelumab trials, would lead NMA results to improve from a tezepelumab perspective (where this data able to be captured for other biologics). Furthermore, from the DESTINATION study, it is known that tezepelumab's one year treatment effect on AAER is sustained in full to the end of year two, not only in the ITT population but also for the subgroups that inform the NMAs used in base case cost-effectiveness analysis (EoS high: ≥300 cells/µl, EoS low: <300 cells/µl, allergic).

- **mOCS reduction**: The mOCS dose reduction period in tezepelumab's SOURCE study (36 weeks) was considerably longer than that of other studies (e.g. mepolizumab SIRIUS

– 16 weeks). Associated to this, patients in SOURCE were permitted multiple attempts to reduce OCS dose (without losing asthma control). This is thought to have contributed to the strong placebo response seen in the trial. In trials of comparators (including SIRIUS), patients were only allowed one attempt to reduce dose. Thus, over a longer timeframe and with multiple attempts to reduce dose (which is more aligned to clinical practice), a stronger placebo response may be observed, meaning the findings of the NMA are likely to be conservative from the perspective of Tezepelumab.

<u>The direction of the NMA is consistent with that of other NMAs, both at the ITT population level and for subgroup NMAs that inform base case</u>

The company base case economic model comparing tezepelumab with other biologics is informed by an NMA which includes two outcomes of interest, AAER and reduction in mOCS dose. The company searched for publicly available NMAs to compare with the one informing the base case.

An externally derived NMA that provides comparative effectiveness on AAER was identified, while no NMA were found for reduction in mOCS dose. Ando K et al.,[8] compared tezepelumab with other biologics and reported results for AAER. The NMA included results for an ITT population as well as some subgroups (NOTE: the subgroup of people with allergic asthma was not included in this publication). Results were reported compared with benralizumab, mepolizumab and dupilumab 300mg (reslizumab and omalizumab were not captured). Although the 300mg dose for dupilumab is not recommended by NICE, this is included in our analysis as a proxy for the 200mg dose recommended by NICE for severe uncontrolled asthma.

The below summary compares the results from Ando K et al., [8] versus the NMA that informs the company base case published in Menzies-Gow et al.,[7] for the outcome of interest. Comparisons are applicable only for the populations and therapies included in both studies.

<u>ITT population:</u>

- Tezepelumab was consistently favourably associated with numerically lower AAERs and ranked first in both NMAs (Ando K et al., and Menzies-Gow et al.,)
- Subsequent favourably ranked treatments varied depending on the publication. Menzies-Gow et al., ranked dupilumab 300mg as the second most favourable treatment in reducing AAER (mean vs tezepelumab: 1.19), while Ando K et al., ranked mepolizumab (mean vs Tezepelumab 1.01).

<u>Sub-group populations</u>:

<u>NMA EoS High (≥300 cells/µl):</u>

This subgroup informs the company base case for the IL-5 eligible population (Note: reslizumab eligible population also includes high EoS as base case, but it is not possible to conduct the comparison between the two NMA studies, as reslizumab is not included in Ando K et al. [8].

- Tezepelumab was favourably associated with numerically lower AAERs, ranking first in both NMAs in this sub-group of people.

- Mepolizumab was the second favourable ranked treatment in both publications followed by benralizumab.
- Tezepelumab was numerically and statistically significant favourably associated with lower AAER compared with benralizumab in Ando K et al., [8].

NMA EoS low (<300 cells/µl):

This subgroup informs the company base case for dupilumab eligible population. The below comparison corresponds to dupilumab 300mg dose as a proxy to dupilumab's 200mg dose.

- Tezepelumab was favourably associated with numerically lower AAERs and ranked first in both network meta-analysis studies in this subgroup (Ando K et al.,[8] and Menzies-Gow et al., ,[7])
- Tezepelumab was also favourably associated with numerically lower AAERs in Menzies-Gow et al., compared with dupilumab 200mg in this subgroup.

Tezepelumab was consistently associated with a numerically lower AAER compared with other biologics in two NMA studies in the ITT population and at subgroup level that informs the company base case. In some of the subgroup comparisons (e.g., EoS High ≥300 cells/µl) tezepelumab also demonstrated statistically significant improvements versus another comparator, indicating a consistent favourability in the outcome of interest versus other biologics.

The company stands by its use of the subgroup NMA for base case as the approach that minimises uncertainty and best reflects treatment practice in England and Wales

The company recognises that in the ideal world, comparisons of tezepelumab to other biologics would be made in the populations that precisely correspond to the biologic eligible populations stemming from NICE's recommendations. However, given the multiple criteria that define biologic eligibility and the fact that the company does not have access to individual patient data for competitor trials, it is not possible to for the company to do this. The company has sought to provide the most relevant comparisons possible given data availability by providing base case analysis using the NMA subgroup data that most closely aligns with eligible populations and by providing sensitivity analysis using an alternative subgroup NMA that could also be deemed to represent the population at hand. In doing so, key treatment effect modifiers are accounted for and so are NICE's eligible populations and therefore clinical practice, as best as is possible.

Uncertainty has further been explored via the use of an alternative NMA, an alternative approach to indirect comparison and by the PSA which simulates all likely parameter values for treatment effect. However, the company believes the current subgroup NMA approach is associated with the least uncertainty and retains this to inform its base case.

4. Utility gain for being on a biologic

In line with the NICE request to remove the additional utility gain associated with biological treatments, the company has removed this assumption in its updated base case analysis.

The utility gain in the model was included on the basis of supportive results from a regression analysis based on the EQ-5D-5L data collected in the tezepelumab clinical trials. When revisiting the mixed

regression utilities model to re-run it without the biologic specific co-efficient, our external vendor identified that an error had been made in the original analysis, relating to subject ID variables. When corrected, the analysis no longer yielded a statistically significant coefficient for biologic-specific utility. As such the original analysis should be regarded as errant.

We apologise for the confusion and have removed the biologic specific utility from all analyses going forwards.

5. Mortality

The company recalls that the ACD notes "*there may be additional benefits of tezepelumab not captured but this is uncertain*". It also states in section 3.15 that "*The clinical expert noted that asthma mortality might be higher than both the company's and the EAG's estimates in clinical practice. He also explained that sometimes mortality does not only occur because of exacerbations but also long-term use of oral corticosteroids*"

The company has conducted a UK real-world study of all-cause mortality in the non-biologic eligible population of this appraisal and uses this to inform its revised base case cost-effectiveness analysis

Based on the comments of the clinical expert at the committee meeting for the current appraisal who stated that asthma mortality might be higher than both the company's and the EAG's estimates, the company has conducted a UK real-world evidence (RWE) study of all-cause mortality in the non-biologic eligible population of interest for this appraisal. The results from this UK RWE study further lend support to results from Roche et al [9], a recently published retrospective observational study of a French healthcare database, which shows all-cause mortality for a cohort of severe uncontrolled asthma patients to be substantially higher than that predicted by the cost-effectiveness model. The combined evidence from the two studies, alongside the comments from the clinical expert at the committee meeting, provides strong evidence for a higher mortality estimate than that currently used in the economic modelling. Based on this, AstraZeneca has updated its base case to include revised mortality estimates from the UK RWE study. The non-biologic eligible population was chosen so that mortality in the standard care (without biologic) arm of the cost-effectiveness model could be calibrated to the findings of the study. In doing so this provides a new mortality 'baseline' in the model, from which mortality for all comparators (including biologics) is derived, via exacerbation-related efficacy inputs.

Methods relating to the UK RWE study are described in full later in this response. In summary, a retrospective cohort study of electronic health records from Clinical Practice Research Datalink (CPRD) linked datasets was undertaken. Patients with severe uncontrolled asthma who had 3 or more exacerbations in the prior year or who were on mOCS and currently ineligible for biologics based on NICE's recommendations, were identified based on clinical characteristics. This population was followed over the period 2012-2017, to capture records of death within the Office for National Statistics (ONS) Death Registration Data. As biologic use is not well captured in CPRD, this follow up period was chosen to align with the timeframe when there was extremely low usage of biologics in the UK (only omalizumab was available and its uptake was very low), meaning the data can be deemed representative of the population treated with standard care without biologic.

The study found all-cause mortality to be considerably higher than that used in the company's cost-effectiveness modelling to date and in keeping with the findings of the Roche et al study. The company plans to develop a manuscript and publish the study.

6. Revised Economic Analyses

A. Methods

Summary of Changes Made to Company's Base Case Analysis

The updates made to the company's base case analysis are summarised in Table 1.

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Table 1: Changes to the company's base case cost-effectiveness analysis

Key issue(s) in the ERG report that the change relates to	Topic	Company's base case within response to technical engagement	Change(s) to base case made in response to ACD	Further information provided in sections that follow this table?
1. Exclusion of reslizumab as a comparator	Reslizumab eligible population	Our initial reading of NICE's technology appraisal guidance for reslizumab was the patients on mOCS were not included in the recommendation, therefore the analysis provided at technical engagement (and at EAG clarification questions) was limited to patients not on mOCS	We now believe the recommendation includes patients on mOCS (providing they also meet other eligibility criteria). Analysis for the reslizumab-eligible population has been updated accordingly	Yes
3. Mismatched subgroups and their provenance in network meta-analyses 1. Exclusion of reslizumab as a comparator	NMAs for the reslizumab eligible population	Base case analyses used the following NMAs: AAER: • Benralizumab - NMA 3+ exacerbations • Mepolizumab - NMA ITT • Reslizumab - NMA 3+ exacerbations OCS sparing: • Benralizumab - NMA ITT • Mepolizumab - NMA ITT	To deliver consistency vs. the NMAs used to inform comparisons in the anti-IL-5 eligible population, the following NMAs are used for base case: AAER: • Benralizumab - NMA EoS High: ≥300 cells/µl • Mepolizumab - NMA EoS High: ≥300 cells/µl • Reslizumab - NMA EoS High: ≥300 cells/µl OCS sparing:	Yes

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		• Reslizumab - Assumption, equal to tezepelumab (due to lack of data)	• Benralizumab - NMA EoS High: ≥300 cells/µl • Mepolizumab - NMA EoS High: ≥300 cells/µl • Reslizumab - Assumption, equal to tezepelumab (due to lack of data)	
3. Mismatched subgroups and their provenance in network meta-analyses	NMAs for the dupilumab eligible population	NMA data relating to the 300mg dose of dupilumab was used in error	NMA data relating to the 200mg dose used – only the 200mg dose is recommended by NICE [10]	No
2. Definition of treatment response	Definition of treatment response	Response defined as any reduction in exacerbations or mOCS dose	Response defined as: • Patients not on mOCS: ≥50% reduction in exacerbations • Patients on mOCS: ≥50% reduction in mOCS dose	Yes
N/A	Unit costs	Unit costs of healthcare resource utilisation reflected the year 2020/21	Unit costs reflect 2022/23	Yes
N/A	Discontinuation probability at response assessment in mOCS treated patients	Assumed to equal that of non-mOCS treated patients	Calculated directly from SOURCE data in population of interest	Yes
8: Asthma mortality may have been overestimated	Exacerbation-related mortality age bands logic	Age band-specific exacerbation-related mortality rates applied up to one year too early in the model. E.g. a patient aged 54.4 years in the model received hospitalised exacerbation-related mortality for the 55-64	Updated such that age band-specific mortality only applied once patient reaches the age corresponding to the lower limit of the age band in question.	No

		years age band (rather than the 45-54 years band)	Please note: The updated approach is applied in the model by selecting Mortality bands = Alternative: 5-year increments	
	Exacerbation-related mortality probabilities	Exacerbation-specific mortality inputs from Watson 2007 [11], Roberts 2013 [12] and 2014 National Review of Asthma Deaths report [13]	Exacerbation-specific inputs uplifted such that outputs align with age-specific real world UK mortality data collected in the non-biologic eligible population of interest	Yes
9. Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events	Utilities	Model informed by utility regression analysis which included biologic-specific treatment effect	Updated utility regression analysis, without biologic-specific treatment effect	Yes

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Reslizumab eligible population

The company's initial reading of NICE's technology appraisal guidance for reslizumab was that patients receiving mOCS were not included in the eligible population. This is because the wording of the recommendation does not specify patients who receive continuous oral corticosteroids [3], whereas the wording of recommendations for other biologics does [1, 2, 14]. Accordingly, the analysis provided at EAG clarification questions and at technical engagement was limited to patients not on mOCS.

However upon further review of the reslizumab guidance we observe that:

- "*a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control*" forms part of the definition of an adequate response to treatment
- When considering reslizumab's cost-effectiveness, the committee concluded that the benefits stemming from OCS sparing had not been captured in the ICER: *"The committee again noted comments from consultees which highlighted the need to see the oral corticosteroid sparing effect of reslizumab being captured in the economic model. It was aware that there are limited data supporting the potential benefits of interleukin-5 inhibitors in reducing oral corticosteroids. The committee concluded that, had the potential benefits of oral corticosteroid sparing been included in the economic analysis, the most plausible ICER for reslizumab could be slightly lower"*

The company now concludes that patients who receive mOCS are eligible for reslizumab, providing they meet its other eligibility criteria; that is, they are adult, have blood EOS count ≥400 cells/μl and had ≥3 exacerbations in the prior year and that the reason mOCS patients are not actively specified in the reslizumab guidance is that there is no need to differentiate between mOCS and non-mOCS treated patients given the same EOS count and prior exacerbations criteria apply to each, whereas for other biologics EOS count and/or prior exacerbations criteria differ according to presence/absence of mOCS treatment, bringing the need to differentiate recommendation wording.

This brought the need to incorporate mOCS treated patients into the reslizumab eligible population for the model for the current appraisal. Analysis of SOURCE trial data showed there to be only 3 patients who were adult, with blood EOS count ≥400 cells/μl and ≥3 exacerbations in the prior year. This would have yielded insufficient data to inform transition probabilities for the model. Given the mOCS treated subset of the anti-IL-5 eligible population reflects patients who are quite similar (adult, with high EOS count), transition probabilities relating to these patients were applied in the model for the reslizumab eligible population treated with mOCS. Resultant transition probabilities can be seen at Table 17. The percentages of patients experiencing a reduction in mOCS for the reslizumab eligible population was assumed to equal those of the anti-IL-5 eligible population as informed by the SOURCE trial, which is presented in Table 110 of the company's submission document. For the reslizumab eligible population as a whole, the percentage of patients treated with mOCS (65%) and the mean mOCS dose at baseline (10mg/day) were assumed to be the same as those of the anti-IL-5 eligible population, as informed by Jackson et al [15].

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Indirect treatment comparison to other biologics

In response to the concern regarding consistency of NMA inputs into the model, base case NMA inputs for the reslizumab eligible population have been updated such that NMA data for the EoS High: ≥300 cells/μl subgroup informs all NMA-based comparisons in this response (comparisons to reslizumab, mepolizumab and benralizumab).

This, in conjunction with the hospitalised AAER NMA no longer being used in the model, means that there is now internal consistency for each comparator in the population which informs NMA data across the endpoints used in the model (AAER and OCS sparing endpoints).

To compliment the base case analysis, the following scenario analyses are provided in this response:

- NMA Alternative Subgroup (AAER only)
  The use of alternative NMA subgroup data that could also be deemed representative of the comparator biologic eligible population, for benralizumab, reslizumab and dupilumab. For mepolizumab, no NMA data for the 3+ exacerbations in prior year population was available, so relative AAER efficacy was assumed to equal that of benralizumab vs. tezepelumab. No alternative NMA data that could be taken to align with the omalizumab eligible population was available, nor alternative NMA subgroup data for OCS sparing endpoints for any comparator, so base case model inputs were used.

- STC ITT
  The use of STC data to inform AAER and OCS sparing endpoints. The methodology used to derive the STC (for AAER, OCS sparing not published) can be found within the publication by Menzies-Gow et al [7]. In summary, individual patient data from tezepelumab trials were used to simulate efficacy estimates within comparator trial populations. An advantage of this approach is that it allows adjustment for multiple factors that are associated with heterogeneity that may affect the treatment comparison (i.e. potential treatment effect modifiers). A disadvantage in the context of the current appraisal is that relative treatment effect is derived in the ITT population of the comparator drug, meaning it is not reflective of NICE eligible populations (and therefore not representative of clinical practice in England and Wales).

  STC data were available to inform all relevant endpoints except for reduction in mOCS dose ≥75%. Here, data for the reduction in mOCS dose ≥90% endpoint was used, as this was more conservative from a tezepelumab perspective than had data for the reduction in mOCS dose ≥50% endpoint been used.

- Ando et al NMA [8] (AAER only)

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> An externally derived NMA that provides comparative efficacy on AAER according to blood eosinophil count for tezepelumab versus benralizumab, mepolizumab and dupilumab 300mg (assumed to be representative of the 200mg dose). No data were available for reslizumab or omalizumab, nor data to inform OCS sparing endpoints for any comparator, so base case model inputs were used.

NMA model inputs for base case and scenario analyses are presented at Table 2 to Table 5.

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Table 2: NMAs used to inform the comparison to other biologics for AAER

Population	Comparator	Base case: NMA Subgroup			Scenario: NMA Alternative Subgroup (AAER only)			Scenario: STC ITT			Scenario: Ando et al NMA [8] (AAER only)		
		Mean	SE	Description	Mean	SE	Description	Mean	SE	Description	Mean	SE	Description
Anti-IL-5 eligible and Reslizumab eligible	Benralizumab	1.670	0.310	NMA EoS High: ≥300 cells/µl	[redacted]	[redacted]	NMA 3+ exacerbations	1.450	0.520	STC ITT	1.969	0.181	NMA EoS High: ≥300 cells/µl
	Mepolizumab	1.120	0.390	NMA EoS High: ≥300 cells/µl	[redacted]	[redacted]	Assumed equal to 3+ exacerbations NMA vs. Benra	1.090	0.400	STC ITT	1.042	0.268	NMA EoS High: ≥300 cells/µl
Reslizumab eligible	Reslizumab	1.430	0.330	NMA EoS High: ≥300 cells/µl	[redacted]	[redacted]	NMA 3+ exacerbations	1.030	0.370	STC ITT	As base case - no data available		
Omalizumab eligible	Omalizumab	1.640	0.400	NMA Allergic	As base case - no logical alternative			1.250	0.340	STC ITT			
Dupilumab eligible	Dupilumab	1.450	0.850	NMA EoS Low: <300 cells/µl	1.190	0.230	NMA EoS High: ≥150 cells/µl	1.042	0.360	STC ITT	1.401	0.204	NMA EoS Low: <300 cells/µl

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Table 3: **NMAs used to inform the comparison to other biologics for reduction in mOCS dose ≥50%**

Population	Comparator	Base case: NMA Subgroup			Scenario: NMA Alternative Subgroup (AAER only)			Scenario: STC ITT			Scenario: Ando et al NMA [8] (AAER only)		
		Mean	SE	Description	Mean	SE	Description	Mean	SE	Description	Mean	SE	Description
Anti-IL-5 eligible and Reslizumab eligible	Benralizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl	As base case - no alternative subgroup NMA data available for OCS sparing endpoints			[redacted]	[redacted]	STC ITT	As base case - no data available for OCS sparing endpoints		
	Mepolizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl				[redacted]	[redacted]	STC ITT			
Reslizumab eligible	Reslizumab	1.000	0.000	Assumption				1.000	0.000	Assumption			
Omalizumab eligible	Omalizumab	1.000	0.000	Assumption				1.000	0.000	Assumption			
Dupilumab eligible	Dupilumab	N/A - eligible population does not include mOCS treated patients											

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Table 4: **NMAs used to inform the comparison to other biologics for reduction in mOCS dose ≥75%**

Population	Comparator	Base case: NMA Subgroup			Scenario: NMA Alternative Subgroup (AAER only)			Scenario: STC ITT			Scenario: Ando et al NMA [8] (AAER only)		
		Mean	SE	Description	Mean	SE	Description	Mean	SE	Description	Mean	SE	Description
Anti-IL-5 eligible and Reslizumab eligible	Benralizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl	As base case - no alternative subgroup NMA data available for OCS sparing endpoints			≥90% reduction STC ITT values used – no STC data available for ≥75% reduction			As base case - no data available for OCS sparing endpoints		
	Mepolizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl									
Reslizumab eligible	Reslizumab	1.000	0.000	Assumption									
Omalizumab eligible	Omalizumab	1.000	0.000	Assumption									
Dupilumab eligible	Dupilumab	N/A - eligible population does not include mOCS treated patients											

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Table 5: **NMAs used to inform the comparison to other biologics for reduction in mOCS dose ≥90%**

Population	Comparator	Base case: NMA Subgroup			Scenario: NMA Alternative Subgroup (AAER only)			Scenario: STC ITT			Scenario: Ando et al NMA [8] (AAER only)		
		Mean	SE	Description	Mean	SE	Description	Mean	SE	Description	Mean	SE	Description
Anti-IL-5 eligible and Reslizumab eligible	Benralizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl	As base case - no alternative subgroup NMA data available for OCS sparing endpoints			[redacted]	[redacted]	STC ITT	As base case - no data available for OCS sparing endpoints		
	Mepolizumab	[redacted]	[redacted]	NMA EoS High: ≥300 cells/µl				[redacted]	[redacted]	STC ITT			
Reslizumab eligible	Reslizumab	1.000	0.000	Assumption				1.000	0.000	Assumption			
Omalizumab eligible	Omalizumab	1.000	0.000	Assumption				1.000	0.000	Assumption			
Dupilumab eligible	Dupilumab	N/A - eligible population does not include mOCS treated patients											

Definition of treatment response

Definition of treatment response was updated for this ACD response. The rationale for the definitions used for base case and scenario analysis is described above. Definitions used are presented in Table 6.

Table 6: Definition of response applied in the model

Population	Base Case	Scenario: Committee requested
Patients not on mOCS	≥50% reduction in exacerbations	
Patients on mOCS	≥50% reduction in mOCS dose	≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations

The resultant transition probabilities that apply in the period following response assessment for base case and scenario analysis can be seen in Table 9 to Table 18.

Unit costs

In all analyses provided by the company prior to this ACD response, unit costs of healthcare resource utilisation reflected the year 2020/21. Unit costs have been updated for this response to capture the additional year of data availability for NHS Cost Collection data (now 2020/21) and to reflect the year 2022/23 via an inflationary multiplier. Annual inflation of 3.08% has been applied, based on the 2020/21 value reported in the Unit Costs of Health and Social Care 2021 [16]. This can be thought of as conservative from the perspective of tezepelumab given current levels of inflation – the UK Consumer Price Index rose by 10.7% for the 12 months to November 2022 [17]. Resultant unit costs for healthcare resource utilisation are provided in Table 7 and mOCS-related adverse event costs are provided in Table 8.

Given the timings of the current appraisal, the earliest possible timing by which the funding mandate for tezepelumab would apply is late July 2023, so there is a strong case that costs should be inflated by a further year to reflect 2023/24, however the company has used 2022/23 so as to be conservative.

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Table 7: Healthcare resource use unit costs

Healthcare resource	Mean	SE	Source
One hour of nurse time	£58.44	£5.84	PSSRU 2021, hourly cost of band 6 nurse [16], inflated to 2022/23 at 3.08% p.a.
GP visit (inpatient)	£41.44	£4.14	PSSRU 2021, 9.22 minute appointment [16], inflated to 2022/23 at 3.08% p.a.
GP visit (home)	£106.91	£10.69	PSSRU 2021, cost of £4.30 informed the per minute cost of patient contact [16]. PSSRU 2013 informed the length of an out of surgery consultation lasting 23.4 minutes. Inflated to 2022/23 at 3.08% p.a.
Nurse visit (outpatient)	£11.69	£1.17	PSSRU 2021, 15 minute GP nurse at £44.00 per hour [16], inflated to 2022/23 at 3.08% p.a.
Nurse visit (home)	£14.61	£1.46	PSSRU 2021, 15 minute with band 6 nurse at £55.00 per hour [16], inflated to 2022/23 at 3.08% p.a.
Respiratory specialist visit (outpatient)	£268.73	£26.87	National Cost Collection 2020/21, weighted average of outpatient consultant led, currency codes WF01A and WF01B, service code 340 [18], inflated to 2022/23 at 3.08% p.a.
Spirometry	£34.73	£3.47	Willson et al [19] inflated to 2022/23 using an inflation index of 1.2315
Flu vaccine	£7.79	£0.78	Willson et al [19] inflated to 2022/23 using an inflation index of 1.2315
Desensitisation of asthma use	£215.97	£21.60	Willson et al [19] inflated to 2022/23 using an inflation index of 1.2315
A&E visit	£131.79	£13.18	National Cost Collection 2020/21, weighted average of emergency medicine, currency codes VB01Z to VB09Z, service code T01NA, T02NA, T03NA and T04NA [18], inflated to 2022/23 at 3.08% p.a.
Hospitalised exacerbation	£3,373.35	£337.34	National Cost Collection 2020/21, weighted average of non-elective long stay, currency codes DZ15M, DZ15N and DZ15P[18], inflated to 2022/23 at 3.08% p.a.

Abbreviations: A&E, Accident and Emergency; GP, general practitioner; PSSRU, Personal Social Services Research Unit; SE, standard error.
All standard errors were assumed to be 10% of the mean value.

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Table 8: mOCS-related adverse event cost by mOCS dose (cyclical cost)

Adverse event		Cyclical cost (£) by mOCS dose (mg/day)					
		0 to <0.5	0.5 to <2.5	2.5 to <5	5 to <7.5	7.5 to <15	>15
Type 2 diabetes mellitus	Mean	£21.65	£22.23	£25.52	£34.21	£32.12	£64.41
	SE	£1.09	£0.54	£1.38	£7.01	£5.58	£26.77
Osteoporosis	Mean	£21.92	£21.48	£21.54	£20.50	£26.57	£98.94
	SE	£0.38	£0.50	£2.37	£1.76	£3.71	£70.74
Glaucoma	Mean	£15.86	£18.08	£18.71	£19.14	£16.70	£14.50
	SE	£0.34	£0.56	£1.04	£1.52	£1.30	£2.48
Cataract	Mean	£33.64	£39.26	£53.90	£55.23	£45.16	£65.67
	SE	£1.42	£2.15	£5.32	£7.48	£8.00	£37.39
Myocardial infarction	Mean	£22.93	£23.35	£28.77	£39.09	£27.33	£68.97
	SE	£0.91	£0.94	£3.29	£7.77	£3.64	£29.41
Heart failure	Mean	£19.87	£22.83	£27.13	£28.69	£30.45	£51.24
	SE	£0.78	£1.09	£2.28	£3.73	£3.90	£25.21
Cerebrovascular accident	Mean	£27.30	£25.95	£32.51	£39.83	£34.70	£83.80
	SE	£1.43	£1.03	£3.69	£8.57	£4.31	£38.09
Renal impairment	Mean	£17.02	£18.36	£21.03	£28.50	£22.07	£33.42

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Adverse event		Cyclical cost (£) by mOCS dose (mg/day)					
		0 to <0.5	0.5 to <2.5	2.5 to <5	5 to <7.5	7.5 to <15	>15
	SE	£0.91	£0.73	£1.94	£6.41	£2.69	£16.27
Peptic ulcer	Mean	£10.68	£13.31	£14.92	£22.15	£18.22	£53.61
	SE	£0.28	£0.85	£0.72	£6.05	£1.71	£30.60
Pneumonia	Mean	£9.36	£14.80	£27.50	£30.05	£35.61	£52.36
	SE	£0.32	£0.46	£2.15	£5.40	£5.00	£14.72

Transition Probabilities

Original transition matrices for each population considered in the model are presented in the company submission Document B, at Table 101 for the anti-IL-5 eligible population, Table 102 for the dupilumab eligible population, Table 103 for omalizumab eligible, and Table 104 for the non-bio eligible (3+ exacerbations OR mOCS). Reslizumab's original transition probabilities (TP) were included in the ERG clarification questions document at Table 23.

Revised base case and scenario analysis TP are presented below at Table 9 to Table 18, whereby base case and scenario reflect the definitions of response as presented at Table 6. Pre-response assessment TP are not provided in this document for the anti-IL-5 eligible, dupilumab eligible, omalizumab eligible and non-bio eligible (3+ exacerbations OR mOCS) populations as the values are not affected by the change in response definition.

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Given the reslizumab eligible population is now deemed to include mOCS treated patients and that data relating to these patients in SOURCE is very limited, pre-assessment with OCS TPs have been assumed to equal those of the anti-IL-5 eligible population (Table 101 Document B). As have post-assessment with OCS TPs, which are presented at Table 17 and Table 18 here, according to response definition.

Pre-response assessment TP are provided here for the reslizumab eligible population, to confirm that the values used in mOCS patients mirror those of the anti-IL-5 eligible population.

Table 9: Base case, transition probabilities (Anti-IL-5 eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

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Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IL, interleukin; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 10: Scenario, transition probabilities (Anti-IL-5 eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]

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Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IL, interleukin; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 11: Base case, transition probabilities (Dupilumab eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	NA	NA	NA	NA
Uncontrolled	NA	NA	NA	NA
Exacerbation (Controlled)	NA	NA	NA	NA
Exacerbation (Uncontrolled)	NA	NA	NA	NA
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				

	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	NA	NA	NA	NA
Uncontrolled	NA	NA	NA	NA
Exacerbation (Controlled)	NA	NA	NA	NA
Exacerbation (Uncontrolled)	NA	NA	NA	NA
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 12: Scenario, transition probabilities (Dupilumab eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)

Controlled	NA	NA	NA	NA
Uncontrolled	NA	NA	NA	NA
Exacerbation (Controlled)	NA	NA	NA	NA
Exacerbation (Uncontrolled)	NA	NA	NA	NA
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	NA	NA	NA	NA
Uncontrolled	NA	NA	NA	NA
Exacerbation (Controlled)	NA	NA	NA	NA
Exacerbation (Uncontrolled)	NA	NA	NA	NA
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]

Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 13: Base case, transition probabilities (Omalizumab eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

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Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

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Table 14: Scenario, transition probabilities (Omalizumab eligible)

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

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Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 15: Base case, transition probabilities (Non-bio eligible [3+ exacerbations OR mOCS])

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				

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	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

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Table 16: Scenario, transition probabilities (Non-bio eligible [3+ exacerbations OR mOCS])

Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

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Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 17: Base case, transition probabilities (Reslizumab eligible)

Tezepelumab: Pre-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Pre-Assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]

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Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mOCS, maintenance oral corticosteroid treatment; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

Table 18: Scenario, transition probabilities (Reslizumab eligible)

Tezepelumab: Pre-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Pre-Assessment without OCS, mean (SE)				

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	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment with OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)

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Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care: Post-assessment without OCS, mean (SE)				
	Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mOCS, maintenance oral corticosteroid treatment; SE, standard error.
Green cells indicate the default state (i.e. if the other transitions do not occur then the model assumes that the cohort will transition to this default state). Grey cells indicate that the transition cannot occur.

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Discontinuation following response assessment

To date in this appraisal, discontinuation probabilities following response assessment for mOCS treated patients have been assumed to equal those of non-mOCS treated patients. For this ACD response, base case probabilities in mOCS patients have been calculated directly from SOURCE data (except for reslizumab eligible patients, for whom discontinuation probabilities have been assumed to equal those of the anti-IL-5 eligible population, owing to insufficient SOURCE data). All discontinuation following response assessment probabilities have been updated to reflect the definition of response now in use for base case and scenario analysis. Resultant probabilities can be seen in Table 19.

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Table 19: Tezepelumab discontinuation probability: 52-week response assessment

Population	Base case definition of response (see Table 6)			Scenario definition of response (see Table 6)		
	Base case approach to discontinuation†		Original approach to discontinuation¶	Base case approach to discontinuation†		Original approach to discontinuation¶
	With mOCS	Without mOCS	With mOCS, Without mOCS	With mOCS	Without mOCS	With mOCS, Without mOCS
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Anti-IL-5 eligible	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab eligible	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Omalizumab eligible	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-bio eligible (3+ exacs OR mOCS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab eligible	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Abbreviations: exacs, exacerbations; IL, interleukin; mOCS, maintenance oral corticosteroid treatment; SE, standard error.
† Discontinuation at response assessment reflects population of interest, derived via data from NAVIGATOR (without mOCS) and SOURCE (with mOCS)
¶ Discontinuation at response assessment in patients with mOCS assumed to equal that of patients without mOCS (the latter derived from NAVIGATOR)

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Exacerbation-related mortality probabilities

Exacerbation-related mortality inputs were restructured into 5-year age bands to allow the model to switch between use of the original mortality estimates and estimates derived using newly available evidence.

The newly available evidence consisted of:

- UK CPRD-ONS study (used for base case)

  A retrospective cohort study of electronic health records from CPRD linked datasets. The (currently) non-biologic eligible patient population was identified based on clinical characteristics and followed over the period 2012-2017, to capture records of death within the Office for National Statistics (ONS) Death Registration Data.

- Roche et al study (scenario analysis)

  A recently published retrospective observational study of a French healthcare database which reports all-cause mortality for a cohort with severe uncontrolled asthma

- Midpoint between original mortality estimates and those of the UK CPRD-ONS study (scenario analysis)

A full explanation of the methodology used in the UK CPRD-ONS study can be found at the Appendix. In summary, a retrospective cohort study of electronic health records from Clinical Practice Research Datalink (CPRD) linked datasets was undertaken. Patients with severe uncontrolled asthma who had 3 or more exacerbations in the prior year or who were on mOCS and were currently ineligible for biologics based on NICE's recommendations, were identified based on clinical characteristics. This population was followed over the period 2012-2017, to capture records of death within the Office for National Statistics (ONS) Death Registration Data. As biologic use is not well captured in CPRD, this follow up period was chosen to align with the timeframe when there was extremely low usage of biologics in UK clinical practice (only omalizumab was available and its uptake was very low), meaning the data can be deemed representative of the population treated with standard care without biologic. Choosing a more recent follow up period (that extended beyond 2017) would have increased the risk of capturing patients on a biologic treatment.

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The UK CPRD-ONS study found all-cause mortality to be considerably higher than that used in the company's cost-effectiveness modelling to date and in keeping with the findings of the Roche et al study (which considered a broader population). The company plans to develop a manuscript and publish the study.

The UK CPRD-ONS study yielded all-cause mortality rates for 10-year age bands (it also yielded 2-year probabilities but these were not used in cost-effectiveness modelling as the rates considered the entirety of the follow-up period and were therefore more robust). Follow-up time was censored based on the minimum of death and registration end date, so it was necessary to transform these rates into probabilities (10 years). Thereafter a multiplier was applied to the original exacerbation-related mortality probabilities, such that the standard care arm of the model for the non-bio eligible (3+ exacerbations OR mOCS) population yielded the same 10-year all-cause mortality probabilities for each age band as mortality probability given by the UK CPRD-ONS study. As the model had been restructured into 5-year age bands, the same multiplier was applied to patients in the first and second half of each 10-year age band. Derivation can be seen in Table 20, whereby (B) is calibrated to (A). As the UK CPRD-ONS study found there to be no mortality in patients aged <50 years, the model slightly over-predicted all-cause mortality in patients of this age even when using a multiplier of zero, because of the general mortality in the model. However since only exacerbation-related mortality leads to meaningful differences in QALYs between intervention and comparators the impact of this was negligible. The study found mortality to be very high in patients aged >90 years, for which a very high calibrating multiplier would have been needed, so a multiplier of ten was used meaning that the model underpredicted (asthma-related) mortality for patients of this age, a conservative approach from a tezepelumab perspective.

These multipliers were retained for cost-effectiveness analysis comparisons to other biologics - in doing so the UK CPRD-ONS study provides a new mortality 'baseline' in the model, from which mortality for all comparators (including biologics) is derived, via exacerbation-related efficacy inputs.

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Table 20: Derivation of exacerbation-related mortality multipliers for the UK CPRD-ONS study (base case)

Age band	UK CPRD-ONS study (base case)		Cost-effectiveness model		
	All-cause mortality rate (N/1000PY)	Calculated 10-year all-cause mortality probability (A)	Multiplier applied to original exacerbation-related mortality probabilities	Cumulative all-cause mortality probability to upper limit of age band	10-year all-cause mortality probability within age band for non-bio eligible population treated with standard care (B)
Patients aged <50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 50 to <60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 60 to <70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 70 to <80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Patients aged 80 to <90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged >90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CPRD, Clinical Practice Research Datalink; N, number of deaths; ONS, Office for National statistics; PY, patient years

A similar calibration process was followed for the scenario analysis that used data from Roche et al. It should be noted that the severe uncontrolled asthma cohort in Roche et al is a broader population than the non-biologic eligible population for this appraisal for which standard care (without biologic) is the appropriate comparator. Despite this, it is the only published study the company is aware of that yields mortality data in an uncontrolled severe asthma population and is therefore of interest. It is likely that the non-biologic eligible population for this appraisal exhibits a higher exacerbation burden (which would serve to increase mortality) but lower blood eosinophil count (likely to decrease mortality) than the all-comer severe uncontrolled asthma cohort studied in Roche et al.

For the severe uncontrolled asthma cohort, the study provided numbers of patients at risk and the number of deaths in a 2-year follow-up period, according to 10-year age bands. From this information, 2-year probabilities of death were calculated and subsequently 10-year probabilities were derived for calibration to the model. Similarly to the UK CPRD-ONS study, Roche et al found there to be no mortality in patients aged <50 years, so a multiplier of zero was used for this cohort. For patients aged >90 years a multiplier of zero was also used - mortality in Roche et al was lower than the general mortality in the model for this age group. Derivation can be seen in Table 21. Multipliers were retained for cost-effectiveness analysis comparisons to other biologics in the same way they were for the base case analysis.

A final mortality-based scenario analysis considers the midpoint between original mortality probabilities and those derived from the UK CPRD-ONS study.

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Table 21: Derivation of exacerbation-related mortality multipliers for the Roche et al study (scenario)

Age band	Roche et al study (scenario)				Cost-effectiveness model		
	Patients at risk	Deaths	2-year all-cause mortality probability	Calculated 10-year all-cause mortality probability (A)	Multiplier applied to original exacerbation-related mortality probabilities	Cumulative all-cause mortality probability to upper limit of age band	10-year all-cause mortality probability within age band for non-bio eligible population treated with standard care (B)
Patients aged <50	166	0	0.0%	0.00%	[redacted]	[redacted]	[redacted]
Patients aged 50 to <60	140	6	4.3%	19.67%	[redacted]	[redacted]	[redacted]
Patients aged 60 to <70	183	15	8.2%	34.79%	[redacted]	[redacted]	[redacted]
Patients aged 70 to <80	136	14	10.3%	41.91%	[redacted]	[redacted]	[redacted]

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Patients aged 80 to <90	86	15	17.4%	61.65%	[redacted]	[redacted]	[redacted]
Patients aged >90	28	9	32.1%	85.61%	[redacted]	[redacted]	[redacted]

Resultant exacerbation-related mortality probabilities by 5-year age band for base case and scenario analyses can be seen in Table 22.

Table 22: Exacerbation-related mortality inputs used in the model

	Original data (restructured to 5-year age bands)	UK CPRD-ONS study (base case)	Roche et al study (scenario)	Midpoint: Original - UK CPRD-ONS (scenario)
OCS burst				
Patients aged <20	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 20 to <25	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 25 to <30	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 30 to <35	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 35 to <40	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 40 to <45	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 45 to <50	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 50 to <55	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 55 to <60	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 60 to <65	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 65 to <70	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 70 to <75	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 75 to <80	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 80 to <85	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 85 to <90	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged >90	[redacted]	[redacted]	[redacted]	[redacted]
A&E visit				
Patients aged <20	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 20 to <25	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 25 to <30	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 30 to <35	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 35 to <40	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 40 to <45	[redacted]	[redacted]	[redacted]	[redacted]

	Original data (restructured to 5-year age bands)	UK CPRD-ONS study (base case)	Roche et al study (scenario)	Midpoint: Original - UK CPRD-ONS (scenario)
Patients aged 45 to <50	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 50 to <55	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 55 to <60	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 60 to <65	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 65 to <70	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 70 to <75	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 75 to <80	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 80 to <85	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 85 to <90	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged >90	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation				
Patients aged <20	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 20 to <25	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 25 to <30	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 30 to <35	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 35 to <40	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 40 to <45	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 45 to <50	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 50 to <55	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 55 to <60	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 60 to <65	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 65 to <70	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 70 to <75	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 75 to <80	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 80 to <85	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged 85 to <90	[redacted]	[redacted]	[redacted]	[redacted]
Patients aged >90	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; CPRD, Clinical Practice Research Datalink; OCS, oral corticosteroids; ONS, Office for National Statistics.

Utilities

Please note that when revisiting the mixed regression utilities model to re-run it without the biologic specific coefficient, our vendor identified that an error had been made in the original analysis, relating to the subject ID variable. When corrected, the analysis no longer yielded a statistically significant coefficient for biologic-specific utility. As such the original analysis should be regarded as errant.

The regression model was re-run without this coefficient, such that only coefficients relating to modelled health states were included in the analysis (and aligned to the request from the committee as stated in the ACD).

The mixed regression model (Table 23) indicated that the utility of a patient without an exacerbation event and with controlled asthma would be [redacted]. The model also indicated that uncontrolled asthma was associated with a utility loss of [redacted]. Patients with an exacerbation event also incurred a change in utility of [redacted] for an mOCS burst, [redacted] for an A&E visit, and [redacted] for hospitalised exacerbation. Goodness of fit statistics are provided at Table 24.

For patients experiencing an exacerbation, the same aggregate utility was applied, irrespective of whether the patient's asthma was previously controlled or uncontrolled, using the setting introduced into the model by the EAG. Utilities were subsequently age-adjusted in the same manner as undertaken previously.

Table 23: Mixed regression model for utility

Variable	Coefficient (95% CI)	p-value
Constant	[redacted]	[redacted]
Uncontrolled asthma	[redacted]	[redacted]
Exacerbation: mOCS burst	[redacted]	[redacted]
Exacerbation: A&E visit	[redacted]	[redacted]
Exacerbation: Hospitalisation	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; CI, confidence interval; mOCS, maintenance oral corticosteroid treatment.

Table 24: Mixed regression model for utility – goodness of fit statistics

Measure	Value
AIC	-43323.02
BIC	-43273.21

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

B. Results

Base case results

In the fully incremental analyses for the anti-IL-5 eligible patients (Table 25) and reslizumab eligible patients (Table 29), tezepelumab was associated with the highest QALYs and lowest costs. As such, tezepelumab, at the PAS price, strictly dominated all comparators. Note that the costs presented for the comparator biologics do not include their respective confidential PAS prices, which if used, would result in different ICERs than those shown.

Base case pair-wise analyses for tezepelumab versus dupilumab and omalizumab are presented in Table 26 and Table 27 respectively. Tezepelumab was dominant versus dupilumab, with QALY gains of [redacted] and cost savings of [redacted] in the dupilumab NICE-recommended population. Similarly, tezepelumab was dominant versus omalizumab, with QALY gains of [redacted] and cost savings of [redacted] in the omalizumab NICE-recommended population. However, the costs presented for the comparator biologics do not include their respective confidential PAS prices and therefore it is acknowledged the ICERs would differ.

Base case pair-wise analysis for tezepelumab versus SoC for the non-bio eligible population is presented in Table 28. Tezepelumab was associated with an incremental cost of [redacted] and a QALY gain of [redacted], resulting in an ICER of £17,251 per QALY gained, below the typically accepted £30,000 per QALY WTP threshold.

Anti-IL-5 eligible population

Table 25: Base case results (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Dupilumab eligible population

Table 26: Base case results (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

Table 27: Base case results (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Non-bio eligible population (3+ exacerbations OR mOCS)

Table 28: Base case results (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,251

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroid treatment; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Reslizumab eligible population

Table 29: Base case results (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,675,499	Dominated
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£184,107	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Sensitivity analyses

Probabilistic sensitivity analysis

The PSA involved undertaking 10,000 simulations, each involving a random draw from each distribution and providing an estimate of the expected costs and QALYs associated with each comparator.

Anti-IL-5 eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs. Results for the comparator biologics were also highly congruent with the deterministic results. Consistent with the base case, tezepelumab dominated both of the comparator biologics considered in the anti-IL-5 eligible population. Table 30 presents the probabilistic incremental cost effectiveness results in detail. The cost-effectiveness scatter plot and frontier can be seen at Figure 1 and Figure 2 respectively.

Table 30: Probabilistic results (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Figure 1: Incremental cost-effectiveness scatter plot (anti-IL-5 eligible)

Abbreviations: Benra, benralizumab; Det, deterministic; Mepo, mepolizumab; PSA, probabilistic sensitivity analysis; Teze, tezepelumab

Figure 2: Cost-effectiveness frontier (anti-IL-5 eligible)

Abbreviations: CE, cost-effectiveness;

Dupilumab eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and 8.072 QALYs whereas dupilumab accumulated total (discounted) costs of [redacted] QALYs, equating to tezepelumab producing an additional [redacted] QALYs with a cost saving of [redacted] versus dupilumab (i.e. being dominant versus dupilumab). The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 31 presents the probabilistic incremental cost effectiveness results. The cost-effectiveness scatter plot and frontier can be seen at Figure 3 and Figure 4 respectively.

Table 31: Probabilistic results (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Figure 3: Incremental cost-effectiveness scatter plot (dupilumab eligible)

Abbreviations: Det, deterministic; Dupi, dupilumab; PSA, probabilistic sensitivity analysis; Teze, tezepelumab

Figure 4: Cost-effectiveness frontier (dupilumab eligible)

Abbreviations: CE, cost-effectiveness.

Omalizumab eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs whereas omalizumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs, equating to tezepelumab producing an additional [redacted] QALYs with a cost saving of [redacted] versus omalizumab (i.e. being dominant versus omalizumab). The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 32 presents the probabilistic incremental cost-effectiveness results. The cost-effectiveness scatter plot and frontier can be seen at Figure 5 and Figure 6 respectively.

Table 32: Probabilistic results (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Figure 5: Incremental cost-effectiveness scatter plot (omalizumab eligible)

Abbreviations: Det, deterministic; Omal, omalizumab; PSA, probabilistic sensitivity analysis; Teze, tezepelumab

Figure 6: Cost-effectiveness frontier (omalizumab eligible)

Abbreviations: CE, cost-effectiveness.

Non-bio eligible population (3+ exacerbations OR mOCS)

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs, whereas SoC accumulated total (discounted) costs of [redacted] and [redacted] QALYs, equating to tezepelumab producing an additional [redacted] QALYs at an incremental cost of [redacted] versus SoC. This results in tezepelumab being cost-effective versus SoC with an ICER of £17,517 per QALY. The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 33 presents the probabilistic incremental cost effectiveness results. The cost-effectiveness scatter plot and frontier can be seen at Figure 7 and Figure 8 respectively.

Table 33: Probabilistic results (non-bio eligible [3+ exacs OR mOCS])

Technology	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,517

Abbreviations: exacs, exacerbations; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroid treatment; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Figure 7: Incremental cost-effectiveness scatter plot (non-bio eligible [3+ exacs OR mOCS])

Abbreviations: Det, deterministic; PSA, probabilistic sensitivity analysis; SoC, standard of care; Teze, tezepelumab

Figure 8: Cost-effectiveness frontier (non-bio eligible [3+ exacs OR mOCS])

Abbreviations: CE, cost-effectiveness; SoC, standard of care.

Reslizumab eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs and was dominant versus all comparators. The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 34 presents the probabilistic incremental cost-effectiveness results. The cost-effectiveness scatter plot and frontier can be seen at Figure 9 and Figure 10 respectively.

Table 34: Probabilistic results (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Reslizumab + SoC	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Figure 9: Incremental cost-effectiveness scatter plot (reslizumab eligible)

Abbreviations: Benra, benralizumab; Det, deterministic; Mepo, mepolizumab; PSA, probabilistic sensitivity analysis; Resli, reslizumab; Teze, tezepelumab

Figure 10: Cost-effectiveness frontier (reslizumab eligible)

Abbreviations: CE, cost-effectiveness

Scenario analyses

Scenario analyses undertaken included:

- Exacerbation-related mortality probabilities:
    - Alternative mortality, Roche et al study
    - Midpoint between original mortality estimates and those of the UK CPRD-ONS study
- ITCs used to inform the comparison to other biologics:
    - NMA Alternative Subgroup (AAER only)
    - STC ITT

    - Ando et al NMA [8] (AAER only)
- Definition of treatment response (single scenario):
    - Patients not on mOCS: ≥50% reduction in exacerbations
    - Patients on mOCS: ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations

Exacerbation-related mortality probabilities: Alternative mortality, Roche et al study

For this scenario, all-cause mortality probabilities in the standard care arm of the model in the non-bio eligible (3+ exacerbations OR mOCS) population were calibrated to those stemming from the study by Roche et al**.**

Anti-IL-5 eligible population

Results can be found in Table 35. Tezepelumab was dominant against both comparators when their list prices were used.

Table 35: Scenario – mortality calibration to Roche et al study (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£452,259	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Dupilumab eligible population

Results can be found in Table 36. Tezepelumab was dominant when dupilumab's list price was used.

Table 36: Scenario – mortality calibration to Roche et al study (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

Results can be found in Table 37. Tezepelumab was dominant when omalizumab's list price was used.

Table 37: Scenario – mortality calibration to Roche et al study (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Non-bio eligible population (3+ exacerbations OR mOCS)

Results can be seen at Table 38. The ICER increased slightly versus base case to become £20,549.

Table 38: Scenario – mortality calibration to Roche et al study (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,549

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroids; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Reslizumab eligible population

Results can be found in Table 39. Tezepelumab was dominant against all comparators when their list prices were used.

Table 39: Scenario – mortality calibration to Roche et al study (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£390,385	Dominated
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£260,470	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Exacerbation-related mortality probabilities: Alternative mortality, Midpoint between original mortality estimates and those of the UK CPRD-ONS study

For this scenario, all-cause mortality probabilities reflecting the midpoint between those that informed the original submission and those stemming from the UK CPRD-ONS study were used.

Anti-IL-5 eligible population

Results can be found in Table 40. Tezepelumab was dominant against both comparators when their list prices were used.

Table 40: Scenario – mortality calibration to midpoint between original mortality estimates and those of the UK CPRD-ONS study (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,330,999	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Dupilumab eligible population

Results can be found in Table 41. Tezepelumab was dominant when dupilumab's list price was used.

Table 41: Scenario – mortality calibration to midpoint between original mortality estimates and those of the UK CPRD-ONS study (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

Results can be found in Table 42. Tezepelumab was dominant when omalizumab's list price was used.

Table 42: Scenario – mortality calibration to midpoint between original mortality estimates and those of the UK CPRD-ONS study (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Non-bio eligible population (3+ exacerbations OR mOCS)

Results can be seen at Table 43. The ICER increased slightly versus base case to become £21,362.

Table 43: Scenario – mortality calibration to midpoint between original mortality estimates and those of the UK CPRD-ONS study (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,362

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroids; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Reslizumab eligible population

Results can be found in Table 44. Tezepelumab was dominant against all comparators when their list prices were used.

Table 44: Scenario – mortality calibration to midpoint between original mortality estimates and those of the UK CPRD-ONS study (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£917,587	Dominated
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£257,693	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

ITCs used to inform the comparison to other biologics: NMA Alternative Subgroup (AAER only)

Anti-IL-5 eligible population

In the base case, the relative exacerbation rate data for the anti-IL-5 eligible cohort was derived from the NMA data for the EOS High: ≥300 cells/μL subgroup. This scenario used the ≥3 exacerbations in last 12 months subgroup NMA data for comparison to benralizumab and assumed the same relative efficacy as this for the comparison to mepolizumab, owing to a lack of subgroup data for mepolizumab. Results can be seen at Table 45. Tezepelumab was dominant against both comparators when their list prices were used.

Table 45: Scenario – Alternative NMA AAER subgroup (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£113,276	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Dupilumab eligible population

In the base case, the relative exacerbation rate data for the dupilumab eligible cohort was derived from the NMA data relating to the EOS Low: <300 cells/μL subgroup. In this scenario analysis the alternative NMA subgroup of EOS ≥150 cells/μl is used. Results can be seen at Table 46. Tezepelumab dominated dupilumab.

Table 46: Scenario – Alternative NMA AAER subgroup (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

A scenario could not be run in this population, as there is no logical alternative subgroup NMA to the allergic subgroup.

Reslizumab eligible population

In the base case, the relative exacerbation rate data for the reslizumab eligible cohort was derived from the NMA data for the EOS High: ≥300 cells/μL subgroup. This scenario used the ≥3 exacerbations in last 12 months subgroup NMA data for comparison to benralizumab and reslizumab and assumed the same

relative efficacy as that versus benralizumab for the comparison to mepolizumab, owing to a lack of subgroup data for mepolizumab. Results can be seen at Table 47. Tezepelumab was dominant against all comparators when their list prices were used.

Table 47: Scenario – Alternative NMA AAER subgroup (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£109,958	Dominated
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£147,386	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

ITCs used to inform the comparison to other biologics: STC ITT

For this scenario, relative efficacy was informed by the STC.

Anti-IL-5 eligible population

Results can be found in Table 48. Tezepelumab was dominant against both comparators when their list prices were used.

Table 48: Scenario – STC ITT (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Dupilumab eligible population

Results can be found in Table 49. Tezepelumab was dominant when dupilumab's list price was used.

Table 49: Scenario – STC ITT (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

Results can be found in Table 50. Tezepelumab was dominant when omalizumab's list price was used.

Table 50: Scenario – STC ITT (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Reslizumab eligible:

Results can be found in Table 51. Tezepelumab was dominant against all comparators when their list prices were used.

Table 51: Scenario – STC ITT (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,565	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

NMAs used to inform the comparison to other biologics for AAER: Ando et al NMA [8] (AAER only)

This scenario analysis is conducted using the NMA AAER values from Ando et al.

Anti-IL-5 eligible population

Results can be found in Table 52. Tezepelumab was dominant against both comparators when their list prices were used.

Table 52: Scenario – alternative NMA AAER subgroup, Ando et al study (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Dupilumab eligible population

Results can be found in Table 53. Tezepelumab was dominant when dupilumab's list price was used.

Table 53: Scenario – Alternative NMA AAER, Ando et al study (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Omalizumab eligible population

A scenario could not be run in this population, as Ando et al did not yield data vs. omalizumab.

Reslizumab eligible population

A scenario could not be run versus reslizumab as Ando et al did not yield comparative data, however it was possible to conduct analysis versus mepolizumab and benralizumab in the reslizumab eligible population. Results can be seen in Table 54. Tezepelumab was dominant against both comparators when their list prices were used.

Table 54: Scenario – Alternative NMA AAER, Ando et al study (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Definition of treatment response: Committee requested

This scenario reflects the following definition of treatment response:

- Patients not on mOCS: ≥50% reduction in exacerbations
- Patients on mOCS: ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations

Transition probabilities (Table 10, Table 12, Table 14, Table 16 and Table 18) and discontinuation following response assessment probabilities (Table 19) are updated accordingly.

Anti-IL-5 eligible population

Results can be seen at Table 55. Tezepelumab was dominant against both comparators when their list prices were used.

Table 55: Committee requested definition of treatment response (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Dupilumab eligible population

As the dupilumab eligible population does not include mOCS treated patients and this scenario only differs from base case in the definition of response in mOCS treated patients, results for this population mirror those of the base case.

Omalizumab eligible population

Results can be found in Table 56. Tezepelumab was dominant when omalizumab's list price was used.

Table 56: Committee requested definition of treatment response (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Non-bio eligible population (3+ exacerbations OR mOCS)

Results can be seen at Table 57. The ICER reduced to £15,762.

Table 57: Committee requested definition of treatment response (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,762

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroid treatment; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

Reslizumab eligible population

Results can be found in Table 58. Tezepelumab was dominant against all comparators when their list prices were used.

Table 58: Committee requested definition of treatment response (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£220,843	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

7. Appendix – UK CPRD-ONS Study Methodology and Results

A. Methodology

Objective

To estimate the all-cause mortality rate and incidence of mortality in patients with severe uncontrolled asthma and 3 or more exacerbations in the prior year or on maintenance OCS, who are not currently eligible for biologic treatment based on NICE technology appraisal guidance for biologics.

Study Design

A retrospective cohort study of electronic health records (EHRs) from Clinical Practice Research Datalink (CPRD) linked datasets.

Data Sources

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Health Service (NHS) and the Medicines and Healthcare products Regulatory Agency (MHRA). It is responsible for providing databases of primary care data (Aurum database) linked to other electronic healthcare data sources. The CPRD Aurum database is a large and representative database consisting of routine primary care EHR, clinical laboratory tests, prescriptions etc. of 20 million patients.

To address the objectives of this study, the following patient level databases are linked through CPRD:

- CPRD Aurum database covering all General Practitioner EHR, prescription details, medical history, lab tests and more.
- Hospital Episodes Statistics (HES Admitted Patient Care data, HES Outpatient, HES Accident and Emergency) covering all hospital visits.
- Office for National Statistics (ONS) Death Registration Data.

Study population

The study will include patients with severe asthma as defined by ERS/ATS guidelines. Patients with severe asthma will be defined as those who have an asthma diagnosis and have received continuous high dose ICS prescriptions and long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA) for at least 12 months.

A cohort of severe asthma patients will be established during the study period from Jan 1, 2012 to December 31, 2017. To enter the cohort, the patients must:

- Be at least 12 years old AND
- Have ≥1 record of asthma diagnosis AND
- Have ≥1 year of medical history in CPRD AND
- Have a record of ≥1 prescription of high-dose ICS AND
- Have recorded continuous use of high-dose ICS along with at least 2 prescriptions of controller (LABA or LTRA) for 12 months

The index date will be the first date of fulfilling all above criteria (severe asthma diagnosis, end of first 12 months of continuous high dose ICS) and patients will be followed up until the end of study period, death or transferred out. The baseline period will be 12 months prior to the index date.

Within the severe asthma cohort, a sub-cohort of uncontrolled severe asthma is identified based on the presence of at least 2 exacerbations in the baseline period. In addition, a sub cohort of patients with severe asthma ineligible for biologics was identified based on the definition outlined in Table 59 (#6). It was not possible to capture fractional exhaled nitric oxide (FeNO) in CPRD, a characteristic pertinent to the dupilumab eligible population, so this characteristic was not accounted for.

The study design is illustrated in Figure 11.

Figure 11: Design of UK CPRD-ONS study

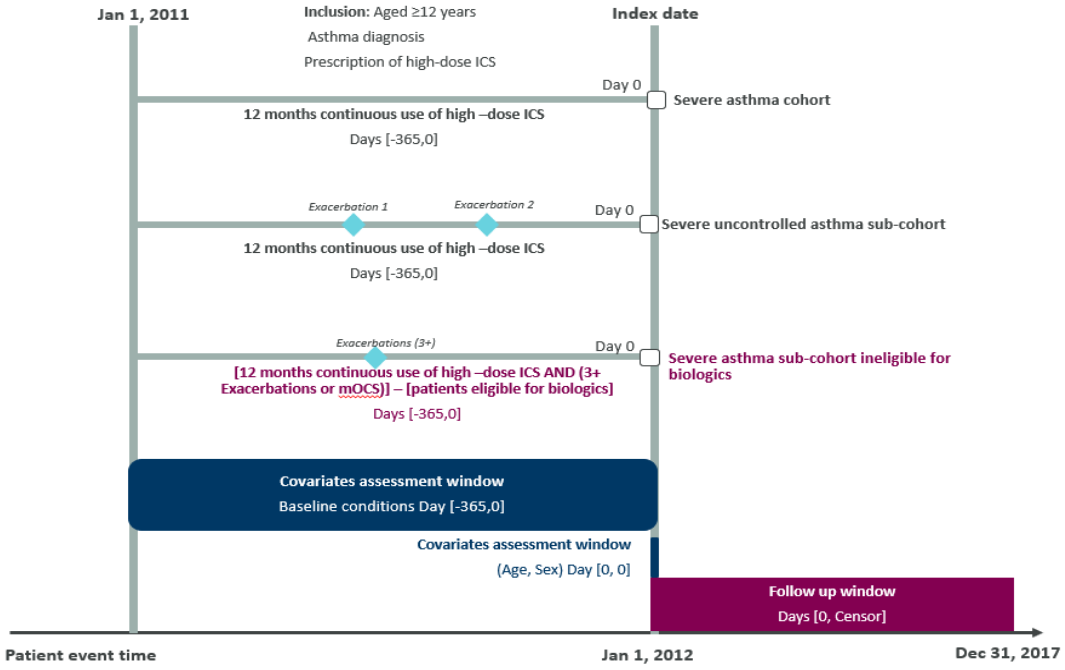

Table 59: Definition of subgroups

Population	Definition	Subgroups
#1	Age 12+ AND High Dose ICS AND (3+ Exacs OR mOCS)	Target population for NICE appraisal
#2	Age 18+ AND High Dose ICS AND {[300+ EOS AND (4+ Exacs OR mOCS)] OR (400+ EOS AND 3 Exacs)}	Subset of target population eligible for mepolizumab, benralizumab
#3	Age 18+ AND High Dose ICS AND 3+ Exacs AND 400+ EOS AND non-mOCS	Subset of target population eligible for reslizumab
#4	Age 18+ AND High Dose ICS AND 4+ Exacs AND 150–299 EOS AND non-mOCS OR Age 12–17 AND High Dose ICS AND 4+ Exacs AND 150+ EOS AND non-mOCS	Subset of target population eligible for first line (biologic) dupilumab
#5	Age 12+ AND High Dose ICS AND Allergic Asthma AND (4+ Exacs OR mOCS)	Subset of target population eligible for omalizumab
#6	#1 minus #2 minus #3 minus #4 minus #5	Subset of target population ineligible for biologics

Abbreviations: EOS, blood eosinophil count, cells/μL; Exacs, exacerbations in prior year; IgE, immunoglobulin E, UI/ml; IL, interleukin; mOCS, maintenance oral corticosteroids

Where mOCS is defined as ≥50% in the baseline period (OCS prescriptions exceeded 180 days over a 12 month period).

Number of exacerbations in previous 12 months prior to index:

Asthma exacerbations were identified using medcodes and prodcodes in CPRD primary care records and with primary diagnosis codes in HES hospital admission records. An exacerbation was defined if the participant experience any of the following:

i. An A&E visit /in- /out-patient hospital admission (i.e., the patient was admitted to the hospital with respiratory (AE) or an asthma medical code for in-out- ICD-10 J45-J46)
ii. Acute OCS treatment (defined as OCS prescriptions lasting ≤ 10 days)
iii. Asthma exacerbation medcode

Exacerbations occurring within seven days of the previous exacerbation episode were not considered a new event. The earliest date among any of the events within a single exacerbation episode was considered as the date of exacerbation.

EOS is defined as the highest record, anytime. The definition of high dose ICS reflects the BTS/SIGN asthma guideline definition [20] and is shown at Table 60.

Table 60: Definition of high dose ICS

Inhaled Corticosteroid	High Dose (µg) [Total Daily Dose Received]
Beclometasone dipropionate (extra fine particle)	500–800 divided in two doses
Beclometasone dipropionate (standard particle)	1200–2000 divided in two doses
Budesonide(dry powder inhalers)	1000–1600 divided in two doses
Ciclesonide (metered dose inhaler)	400–640 divided in two doses
Fluticasone furoate	200 as a single dose
Fluticasone propionate (metered dose and dry powder)	600–1000 divided in two doses
Mometasone furoate	>400 up to 800 divided in two doses

Patients who also had a diagnosis for COPD were excluded from the analysis, as were patients with major respiratory diagnoses including cystic fibrosis, pulmonary fibrosis, bronchiectasis, respiratory tract cancer, bronchopulmonary dysplasia, sarcoidosis, lung cancer, interstitial lung disease, pulmonary hypertension, and tuberculosis ever.

B. Results

The subject flow can be seen at Table 61.

376 patients had severe uncontrolled asthma with 3 or more exacerbation in the prior year or were on maintenance OCS and were ineligible for biologic therapy.

Table 61: Subject Flow

		All
Continuous ICS for 12 months 2012-2017		[redacted]
		[redacted]
Along with 2 controllers for 12 months		[redacted]
		[redacted]
Asthma diagnosis ever		[redacted]
		[redacted]
More than 1-year medical record prior to the index date	n (missing)	[redacted]
	Excluded	[redacted]
	Included	[redacted]
		[redacted]
Death before index date	n (missing)	[redacted]
	Included	[redacted]
	Excluded	[redacted]
		[redacted]
No COPD	n (missing)	[redacted]
	Included	[redacted]
	Excluded	[redacted]
		[redacted]
Other exclusions	n (missing)	[redacted]
	Included	[redacted]
	Excluded	[redacted]
		[redacted]

		All
With linked HES data (includes other exclusion criteria)	n (missing)	[redacted]
	Excluded	[redacted]
	Included	[redacted]
		[redacted]
Age 12+ and Severe Asthma		[redacted]
Age 12+ and Severe Uncontrolled Asthma		[redacted]
Target population for NICE appraisal		[redacted]
Subset of target population eligible for mepolizumab or benralizumab		[redacted]
Subset of target population eligible for reslizumab		[redacted]
Subset of target population eligible for dupilumab		[redacted]
Subset of target population eligible for omalizumab		[redacted]
Subset of target population ineligible for biologic		[redacted]

All-cause mortality findings for the biologic ineligible population can be seen at Table 62.

Table 62: Findings for target population ineligible for biologic therapy

		All
Subset of target population ineligible for biologic		[redacted]
1 year mortality		[redacted]
2 year mortality		[redacted]
Death entire follow up		[redacted]
Mortality rate (N/1000PY)		[redacted]
Age (years)	n (missing)	[redacted]
	Mean (SD)	[redacted]
	Median (IQR)	[redacted]
	Min - Max	[redacted]
Gender	n (missing)	[redacted]
	Male	[redacted]
	Female	[redacted]
Age bands	n (missing)	[redacted]
	<20	[redacted]
	20-30	[redacted]
	30-40	[redacted]
	40-50	[redacted]
	50-60	[redacted]
	60-70	[redacted]
	70-80	[redacted]
	80-90	[redacted]
	>90	[redacted]
2 year mortality: Age 50 to <60		[redacted]
Mortality rate (N/1000PY): Age 50 to <60		[redacted]
2 year mortality: Age 60 to <70		[redacted]
Mortality rate (N/1000PY): Age 60 to <70		[redacted]
2 year mortality: Age 70 to <80		[redacted]
Mortality rate (N/1000PY): Age 70 to <80		[redacted]
2 year mortality: Age 80 to <90		[redacted]
Mortality rate (N/1000PY): Age 80 to <90		[redacted]

		All
2 year mortality: Age >=90		[redacted]
Mortality rate (N/1000PY): Age >=90		[redacted]
2 year mortality male		[redacted]
2 year mortality female		[redacted]
Age at death (All)	n (missing)	[redacted]
	Mean (SD)	[redacted]
	Median (IQR)	[redacted]
	Min - Max	[redacted]
Age at death (Death within 2 years)	n (missing)	[redacted]
	Mean (SD)	[redacted]
	Median (IQR)	[redacted]
	Min - Max	[redacted]

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NICE National Institute for Health and Care Excellence

Tezepelumab for treating severe asthma [ID3910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 January 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • Has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Allergy & Clinical Immunology (BSACI)
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Tezepelumab for treating severe asthma [ID3910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 January 2023. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Tezepelumab inhibits the activity of the alarmin TSLP, the first biological agent available for the treatment of asthma to do so. Anti-IL-33 has also recently become available. Release of TSLP, along with the alarmins IL-33 and IL-25 locally in the airways from epithelial cells subject to environmental damage in turn induces local release of asthma-relevant cytokines, particularly IL-5, form local, type 2 innate lymphoid cells. Th2-type T lymphocytes, induced to differentiate because of the local Th2-type cytokine release, contribute to this local production of IL-5 and also the local differentiation of B lymphocytes into IgE-secreting plasma cells. Thus, the alarmins stand upstream of IL-5 and other Th2-type cytokines in the inflammatory cascade which drives airways inflammation and remodelling in asthma, as well as bronchospasm which is exacerbated by products of eosinophils, such as cationic proteins, acting on the Calcium-Sensing receptor on airways smooth muscle cells, over-expression of which is now known to mediate bronchial smooth muscle hyperresponsiveness (discussed in Riccardi D et al. Eur Resp J 2022 Aug 10; 60(2):2102103. doi: 10.1183/13993003.02103-2021). All three alarmins induce remodelling of the airways epithelium and may ultimately be responsible for irreversible airways obstruction which develops in some patients with asthma and may increase symptomatology and reduce airways patency in a corticosteroid-resistant fashion. There is apparently no provision in any of the clinical trials referred to in this analysis for the definition and identification of patients with irreversible airways obstruction which may be contributing to symptomatology and which will be resistant to corticosteroids and biological therapies alike.
2	Following on from point 1, it is likely that anti-alarmin biological therapies for asthma will be most appropriate in the future as prophylactic treatment to prevent airways remodelling and irreversible obstruction in patients identified as being at risk: biomarkers designating such patients, if and when they are defined, will likely comprise the true biomarkers dictating the appropriateness of therapy with biological agents.
3	Key clinical issues (slide 2): NMAs. Since there is no accepted protocol to define the inherent variability of blood eosinophil counts and FeNO within a given individual patient with asthma and how these may vary according to the time of day and the timing of and compliance with prescribed therapy, particularly topical and systemic glucocorticoid, it seems premature to assume that these markers measured on a single occasion are of any clinical significance even if differences between groups of patients can be demonstrated retrospectively in single, cross-sectional meta-analyses.
4	Slide 7. There is arguably no such thing as “Allergic IgE mediated asthma”. Type 1 hypersensitivity to inhaled aeroallergens may exacerbate asthma symptoms in patients who are clinically sensitised, but this is a minor contribution to symptomatology as demonstrated by the lack of therapeutic effect of anti-histamines. Omalizumab likely reduces the rate of exacerbation of asthma principally by restoring innate immunity to respiratory tract viral infection (discussed in Riccardi D et al. Eur Resp J 2022 Aug 10; 60(2):2102103. doi: 10.1183/13993003.02103-2021).
5	Key clinical issues (slide 2): Correct inhaler technique, as well as perfect compliance when delivering topical therapy to the airways of asthmatics may have profound effects on symptomatology and “exacerbation” of asthma (see Dekhuijzen PNR et al. J Allergy Clin Immunol Pract 2022 Jul;10(7):1813-1824.e1. doi: 10.1016/j.jaip.2022.03.013) and is considered in none of the studies included in this analysis. Groups of patients randomised to receiving, or not receiving regular,

Tezepelumab for treating severe asthma [ID3910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 January 2023. Please submit via NICE Docs.

	effective tuition in using suitable inhaler devices and encouragement to comply as requested with therapy should ideally be included as additional "placebo" groups in trials of the possible effects of biological therapies if their true worth in relationship to "conventional" therapies is to be evaluated, otherwise the contribution of these factors to poor asthma control, which may be considerable, cannot be evaluated.
6	As remarked already in slide 8 (for example), an acceptable treatment "response", in terms of symptomatology, symptom frequency and period of observation (and in addition to having eliminated poor inhaler technique and/or compliance as possible contributors) remains to be defined.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**SANOFI**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	On paragraph 3.4 the proposed population for tezepelumab includes those who are having maintenance oral corticosteroids. In the SOURCE study, however, tezepelumab did not meet its primary endpoint of a categorised percentage reduction in final daily oral corticosteroid dose at week 48 versus placebo. Also, the odds of achieving a category of greater percentage reduction in daily maintenance oral corticosteroid dose at week 48 were higher, but not significantly in the tezepelumab group than in the placebo group in patients with a baseline blood eosinophil count of at least 150 cells per µL, which is consistent with a previous oral corticosteroid-sparing study of an asthma biologic. Given the available evidence, we believe additional data for severe asthma patients who are dependent on maintenance oral corticosteroids is required to ensure that tezepelumab is an appropriate intervention for this cohort.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Thoracic Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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2	3.6 Treatment response We feel that treatment response should be defined as a 50% reduction in exacerbation frequency OR a 50% reduction in maintenance oral corticosteroid dose within the first 12 months. This is the criteria by which response to other biologics are assessed. We agree that the company's definition of treatment response was not appropriate.
3	3.12 We agree with using an ACQ-6 score of 1.5 as a cur-off to define asthma control status with ACQ-6 score >1.5 indicating uncontrolled asthma
4	3.15 Mortality estimate Mortality related to (severe) asthma is likely to be underestimated as it is much more likely to be related to side effects from long-term and cumulative use or oral corticosteroids, which would not be collected through Health Survey and Registry data, than to acute exacerbations of asthma.
5	3.16 Assuming utility gain We disagree with the committee. There is a statistically significant difference in EQ-5D-5L and therefore this should not be ignored.
6	3.18 Further analyses needed: Treatment response should be defined as 50% reduction in exacerbations OR systemic corticosteroid dose and not 'AND'. This is in line with currently licenced biologics (mepolizumab and benralizumab), reflects clinical practice across UK severe asthma centres and the severe asthma toolkit (co-developed by NHS England)

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England Specialised Commissioning
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Asthma + Lung UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**We have no links to the tobacco industry and our internal guidelines would prevent this**.
Name of commentator person completing form:	[redacted]

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1	Previous appraisals have taken into account the additional utility gain of biological treatments for people with severe asthma, which in our view is significant. This committee has decided not to take this additional utility gain into account for Tezepelumab, and we disagree with this approach. Severe asthma is often debilitating and severely impacts quality of life, mental health and wellbeing. We know that it results in people feeling isolated, lonely, anxious and fearful, and that it impede their ability to do activities like going to work or participating in physical activity. People with severe asthma have told us that: *"Trying to hold down my job and live my life as normally as possible is nearly impossible. Before I was diagnosed with severe asthma, I was an active, happy person who enjoyed the outdoors, spending time with my dog and my horse, and seeing my friends regularly. Now I'm clinging on to my part-time job and am too scared to leave the house in case I have an asthma attack. I live with my mum and on my bad days she is basically my carer..."* *(Fighting Back Report, pg.16)* *"… I spent all the time in hospital. The first few times you get admitted, everybody comes to see you. But then, it gets a little bit boring and out of the way. So, friendships drift off and fall into a bit of isolation, really."* *(Do No Harm Report, pg.14),* It is clear that biologic treatments can have a dramatic and transformative impact and significantly change the quality of life for many of those who receive them. In our 2021 *'Do No Harm'* severe asthma report, we found that: • 43% of respondents with severe asthma said that a biologic had improved their quality of life • 23% said that it's been completely life-changing • 13% also revealed that they are less anxious/scared as a result of a biologic treatment. In our most recent *'Fighting Back'* report we also hear about the wider benefits that people with severe asthma have experienced because of biologic treatments – one supporter told us: *"Biologic drugs have given me my life back. I noticed a huge improvement almost immediately and haven't needed to take steroids since. I can now exercise and have regained my independence and social life..."* Similarly, we conducted six interviews of people with severe asthma in England in our *Falling into Isolation Report*. Participants stated that: *"I just wish I had been put on this biologic a lot sooner. Because the period I was suffering, you can't explain it in words. It was really, really hard for me. It was just so depressing that sometimes you think your life is just not worth living anymore."* *Participant 1* *"What [the biologic] has also done is give me a sense of confidence…It has just provided that extra dimension of freedom, a psychological freedom, really. That's an invaluable thing. It's a really basic thing, not being sick all the time".* *Participant 3*

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	"Well, I actually have a life now, because before I was on a mobility scooter. I was unable to do anything. I wasn't able to leave the house without the scooter. I just had no life. So, yes, it's come back now". *Participant 5* It is clear that the introduction of biologics can be truly transformational for people with severe asthma. However, not everyone is currently able to benefit from biologic drugs based on clinical biomarkers (FeNO, Blood eosinophils & IgE levels). Tezepelumab however, could change this and has demonstrated improvement in patient outcomes in a broad population of severe asthma patients regardless of clinical biomarker levels. There is a large unmet need in the UK amongst patients that do not meet the eligibility criteria for available biologics. This group carries a significant overall burden of disease, with frequent exacerbations and poor quality of life, yet are unable to receive current biologics. The patient population in question sits at step 5 on the BTS/SIGN guidelines, and therefore are the most severe population of asthma patients. They have the highest disease burden, especially as they must have had 3 or more exacerbations or be on maintenance oral steroids to be eligible for treatment and this population is at a much greater risk of future asthma attacks, hospital visits and therefore possible death. We view Tezepelumab as an big opportunity to improve patient outcomes within this population, and regard the additional utility gain within this group as a significant and important part of Tezepelumab's impact. Given the severity of symptoms experienced by this group, the potential utility gain is significant, and we believe that it should be taken into account fully.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**] Patient Expert
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**] None
Name of commentator person completing form:	[**Insert your name here**] Anne Little

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Given the recommendations, I am quite concerned that 65% of uncontrolled severe asthmatics, particularly **those who do not qualify for other biologics will not have the opportunity to try, and potentially benefit from, using Telezumab**.
2	Although I am not a numbers person, I can grasp the rationale for needing a clear definition of 'controlled' severe asthma in order to measure/analyse treatment outcomes and keep trials on a certain trajectory. However, **I just wonder if there is a risk of definitions becoming rigid to the point where patients who might benefit, lose out**?
3	Expanding on 2… **is there scope for a little more qualitative data from patients on what is meant by a 'meaningful reduction in exacerbations'**?
4	**What really strikes me about Telezumab is that it targets the top of the inflammatory cascade. If this is the case, could the drug have long term health benefits for all severe asthmatics beyond those offered by other biologics?** I am not an expert by any means, but if Telezumab intervenes at the top of the inflammatory cascade does this mean it has the potential to stick a spanner in the works before airway re-modelling processes leading to long term damage become established?
5	Expanding on 4… **could Telezumab be a more cost efficient treatment for severe asthma than other biologics?**
6	

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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) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
Authors	**Madhusubramanian Muthukumar**[1] **Helen Coelho**[1] **Edward CF Wilson**[1] **Naomi Shaw**[1] **Rebecca Bilden**[1] **G.J. Melendez-Torres**[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
Correspondence to	G.J. Melendez-Torres 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
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St Luke's Campus
Heavitree Road
Exeter
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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.

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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

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