Single Technology Appraisal

Tezepelumab for treating severe asthma [ID3910]

Appraisal Committee Meeting – 08 November 2022

First committee meeting

The following documents are made available

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from Astrazeneca

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Thoracic Society
   b. NHS England and Improvement (Specialised Commissioning)

4. **External Assessment Report** prepared by PenTAG

Post-technical engagement documents

5. **Technical engagement response from company**

6. **Technical engagement responses from stakeholders:**
   a. British Society for Allergy & Clinical Immunology (BSACI)
   b. Asthma + Lung UK (A+LUK)

7. **External Assessment Report critique of company response to technical engagement** prepared by PenTAG

8. **Appraisal Committee Meeting presentation slides** – to follow

Please note that the full submission, appendices to the company's submission, and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tezepelumab for treating severe asthma (ID3910)

Document A

Company evidence submission summary for committee

AstraZeneca confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

File name	Version	Contains confidential information	Date
ID3910_Tezepelumab_Document A_[ACIC Fully Redacted]	**V1.0**	**Yes**	**24th May, 2022**

Contents

Submission summary

A.1 Health condition – B.1.3 (page 22)

Asthma is a heterogeneous disease, characterised by chronic airway inflammation, and defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity together with variable expiratory airflow limitation (1). Severe asthma is defined as asthma that remains uncontrolled despite optimised treatment with high dose inhaled corticosteroid in combination with a long-acting beta-agonist (ICS-LABA), or that requires high dose ICS-LABA to prevent it from becoming uncontrolled (1). Of the 5.4 million patients receiving treatment for asthma in the UK (2), it is estimated that around 4% have severe asthma (3), of which 65.5% (or 141,000 people) have severe, uncontrolled asthma (4).

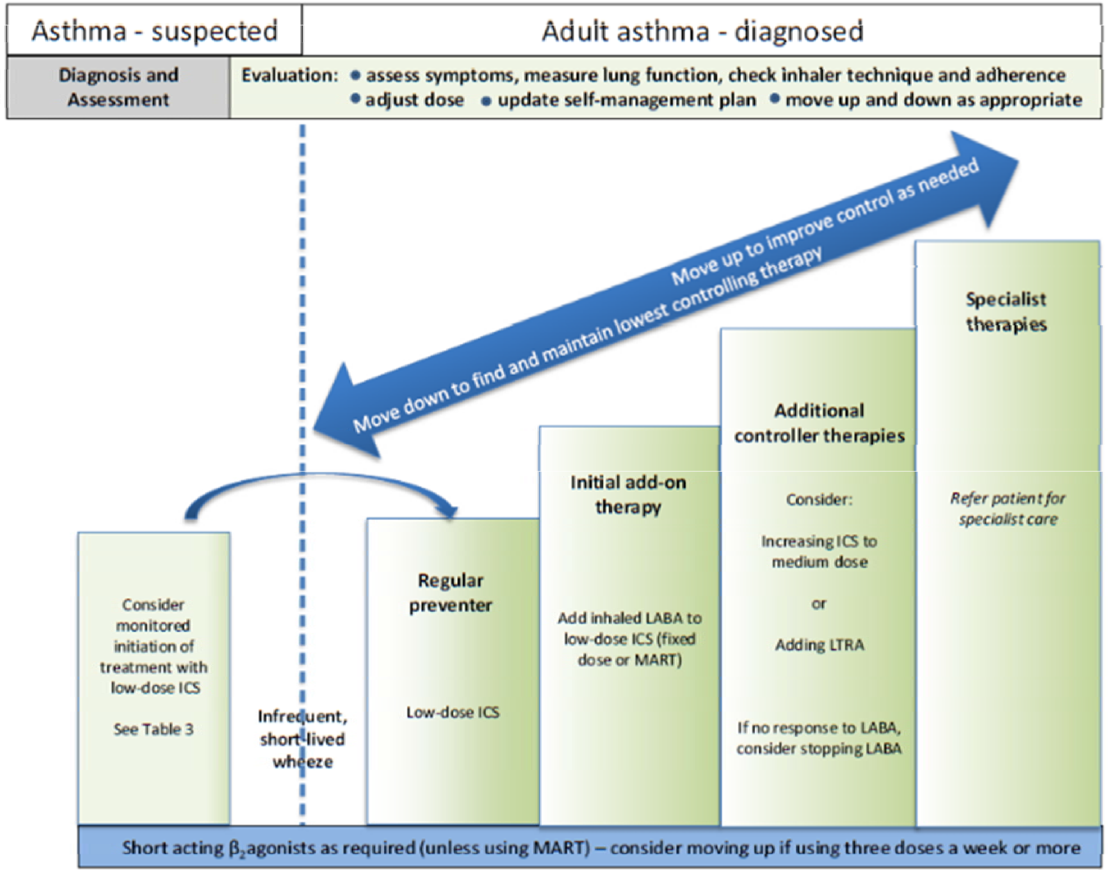
The burden of severe, uncontrolled asthma is high due to associated exacerbations and hospitalisations (5). The unpredictability and distress associated with severe, uncontrolled asthma symptoms has a substantial negative impact on the lives of patients, including a detriment in the ability to perform usual daily activities (1, 6, 7) and negatively impacts their mental health (8). Patients with asthma have a higher mortality rate compared with patients with non-severe asthma (9). A 2019 analysis of Office for National Statistics (ONS) data by Asthma UK revealed that overall, more than 12,700 people died from asthma in England and Wales over the past decade, with deaths increasing by 33% between 2008 and 2018 (10). Healthcare costs per patient with severe asthma are higher than those for patients with type 2 diabetes, stroke or chronic obstructive pulmonary disease (COPD) (1, 11). In a 2017 UK study using data from a nationally representative primary care database, the Optimum Patient Care Research Database (OPRCD), the average healthcare costs per person per year with severe asthma ranged from £2,603 to £4,533 (12).

A.2 Clinical pathway of care – B.1.3.6 (page 29)

In England, treatment for severe, uncontrolled asthma generally follows the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines (13), presented in Figure 1. According to BTS/SIGN guidelines, adults with asthma not adequately controlled on the recommended initial or additional controller therapies should be considered for specialist therapies, including high dose ICS, leukotriene receptor antagonist (LTRA), tiotropium bromide, or theophylline (13). Add-on biologic therapies may also be considered, with the choice of biologic prescribed depending on the patient's asthma phenotype and biomarker profile (13).

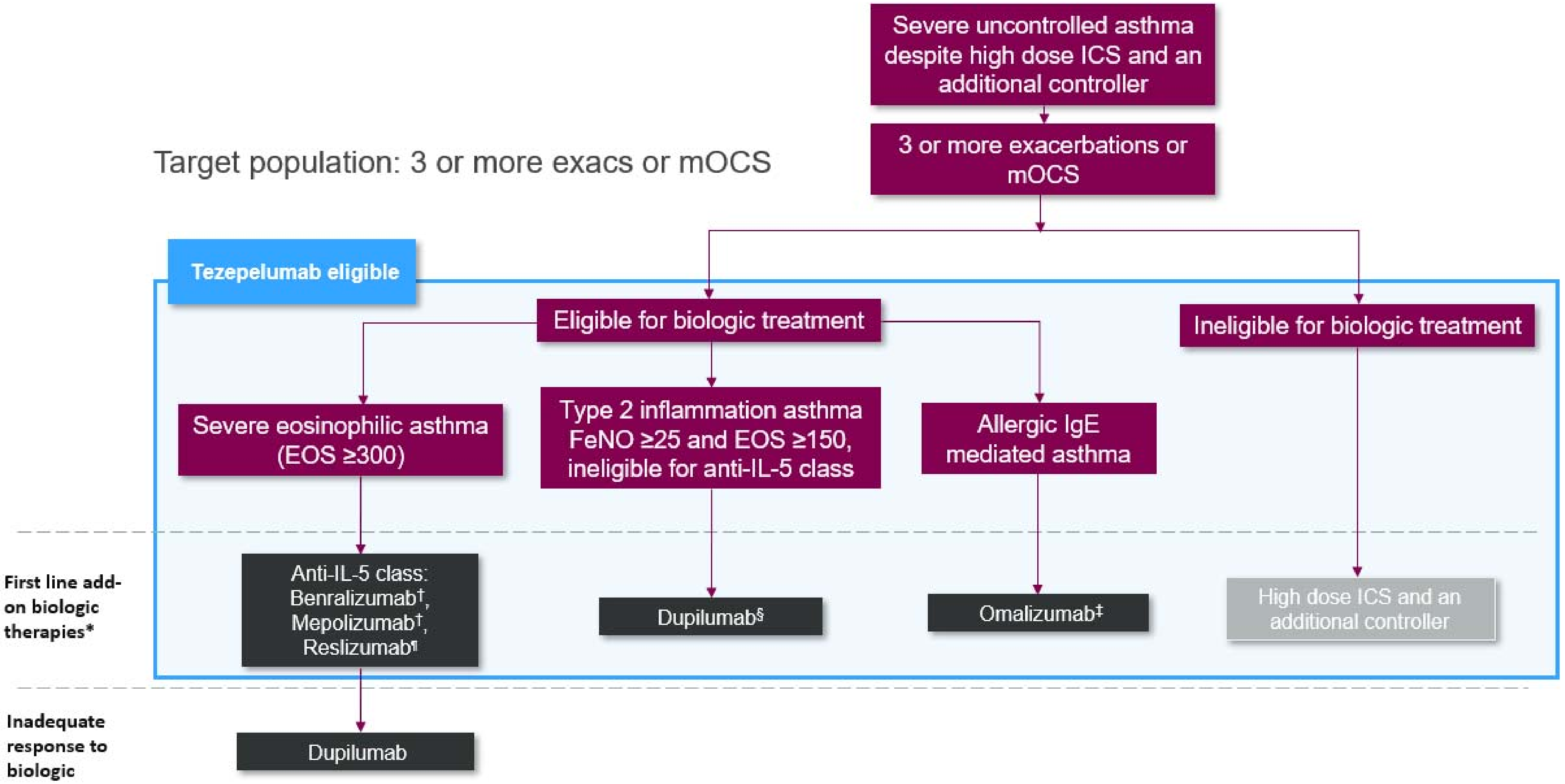
Figure 2 outlines the proposed positioning of tezepelumab within the biologic therapy pathway of care for severe asthma patients. The company submission positions tezepelumab as a treatment for adults and adolescents 12 years and older with severe uncontrolled asthma patients despite high dose ICS and an additional controller, who have had 3 or more exacerbations in the prior year, or who are on maintenance oral corticosteroid (mOCS), irrespective of biomarker values. Introducing tezepelumab in this setting will provide access to a biologic treatment for some patients who are currently ineligible and provide an additional first line treatment option for patients who are currently eligible for biologic treatment, with a different mode of action that targets higher up in the inflammatory cascade.

Figure 1: BTS/SIGN – 2019 guideline for the management of asthma in adults/adolescents



Abbreviations: BTS, British Thoracic Society; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; SIGN, Scottish Intercollegiate Guidelines Network.

Figure 2: Proposed positioning of tezepelumab in the treatment of patients with severe uncontrolled asthma



Abbreviations: EOS, eosinophil; exacs, exacerbations; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; mOCS, maintenance oral corticosteroid treatment.

† Adults: (400+ EOS AND 3+ exacs) OR 300+ EOS AND (4+ exacs OR mOCS)

¶ Adults: 400+ EOS AND 3+ exacs

§ (Adults: 25+ FeNO AND 150-299 EOS AND 4+ exacs) OR (Age 12-17: 25+ FeNO AND 150+ EOS AND 4+ exacs)

‡ Age 6+: Allergic IgE-mediated asthma AND 4+ exacs OR mOCS

* Add-on to high dose ICS + additional controller.

A.3 Equality considerations – B.1.4 (page 44)

A recommendation for tezepelumab in patients with severe, uncontrolled asthma who have experienced 3 or more exacerbations in the prior year OR who require mOCS, addresses existing inequality in two main ways:

1. Equality for patients who do not meet biomarker criteria for current biologics: There is currently no biologic treatment option for patients with low eosinophilic, low fractional exhaled nitric oxide (FeNO), non-allergic severe asthma. A recommendation in a broader population will address this and provide a therapy option for thousands of severe asthma patients who are currently ineligible to receive a biologic to help manage their condition.
2. Gender equality: Severe asthma is a condition that is known to have a higher prevalence among females compared with males; throughout their lifetime, females have a higher likelihood of developing asthma and developing a more severe form of asthma than their male counterparts (14). This is supported by the demographics in the tezepelumab NAVIGATOR trial, in which 63.5% of subjects were female. Furthermore, patients with non-eosinophilic phenotypes of severe asthma are more likely to be women when compared with the breakdown by gender of patients with an eosinophilic subtype (81.5% versus 62.9%; p=0.047) (15). With women suffering from non-eosinophilic disease more than men, the reimbursement of tezepelumab across a broad severe asthma patient population, regardless of biomarkers, helps to address the current inequality that exists in terms of biologic treatment options for women.

A.4 The technology – B.1.2 (page 21)

Table 1: Technology being appraised

UK approved name and brand name	UK approved name: Tezepelumab Brand name: [redacted]†
Mechanism of action	Tezepelumab is an anti-TSLP, human monoclonal antibody (IgG2λ) that binds to human TSLP with high affinity and prevents its interaction with the heterodimeric TSLP receptor.

	TSLP, an epithelial cell-derived cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, and inducing downstream inflammatory processes and bronchial hyper-responsiveness. TSLP has also been shown to have indirect effects on airway structural cells (e.g. fibroblasts and airway smooth muscle). In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with inflammation (e.g. blood EOS, IgE, FeNO, IL-5, and IL-13).
Marketing authorisation/CE mark status	CHMP positive opinion is anticipated in [redacted]. MHRA MA is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The draft indication covered in the submission is as follows: [redacted].
Method of administration and dosage	[redacted]
Additional tests or investigations	None.
List price and average cost of a course of treatment	List price: [redacted] per vial Average cost of a course of treatment: Lifetime treatment for responders, 1 year of treatment for inadequate responders
Patient access scheme (if applicable)	A simple PAS has been submitted to PASLU with a net price of [redacted] per vial

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; TSLP, thymic stromal lymphopoietin.
† Subject to approval.

A.5 Decision problem and NICE reference case – B.1.1 (page 17)

The company submission covers a subset of the technology’s (anticipated) marketing authorisation.

- The (draft) tezepelumab indication is: [redacted].
- This submission covers: Adults and adolescents 12 years and older with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year OR are on mOCS.

Table 2 summarises the decision problem addressed by the submission.

Table 2: The decision problem – B.1.1 (page 18)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years or older with severe asthma that is inadequately controlled by standard therapy	Adults and adolescents 12 years and older with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year OR are on mOCS	The target population reflects where tezepelumab provides the greatest absolute clinical benefit
Intervention	Tezepelumab as an add-on to standard therapy	As per scope	NA
Comparator(s)	For people for whom biologics are indicated or suitable according to NICE guidance, in addition to standard therapy: • Reslizumab • Benralizumab • Mepolizumab • Omalizumab	As per scope with the exception of reslizumab + SoC	Reslizumab + SoC was excluded as a comparator in economic modelling on the basis of it not representing established NHS practice in the target population. See Section B.3.2.3.2 in Form B for further details.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	- Dupilumab (subject to ongoing NICE appraisal) For people for whom currently available biologics are not indicated or suitable: - Optimised standard therapy without biologics		
Outcomes	The outcome measures to be considered include: - Asthma control - Incidence of clinically significant exacerbations, including those that require unscheduled contact with healthcare professionals or hospitalisation - Use of oral corticosteroids - Patient and clinician evaluation of response - Lung function - Mortality - Time to discontinuation - Adverse effects of treatment - Health-related quality of life	As per scope	NA
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: - Baseline EOS levels - Baseline FeNO levels - People who require maintenance OCS treatment - People who require frequent OCS treatment	As per scope. In addition, the following subgroups are considered: - The anti-IL-5 eligible population: – Age 18+, 300+ EOS (4+ exacs OR mOCS) OR (400+ EOS AND 3 exacs) - The omalizumab eligible population: – Age 12+, 30+ IgE AND (4+ exacs OR mOCS)	To enable assessment of clinical and cost-effectiveness in the subpopulations in which NICE's recommendations from previous biologic appraisals apply and remaining patients with 3 or more exacs or mOCS who are currently not biologic eligible

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		• The dupilumab eligible population: – Age 18+ AND 4+ Exacs AND 150–299 EOS AND 25+ FeNO AND non-mOCS, OR – Age 12–17 AND 4+ Exacs AND 150+ EOS AND 25+ FeNO AND non-mOCS • The 3+ exacs or mOCS non-bio eligible population (people for whom currently available biologics are not indicated or suitable): – Age 12+ AND 3+ exacs OR mOCS minus anti-IL-5 eligible minus omalizumab eligible minus dupilumab eligible	
Special considerations including issues related to equity or equality	None	Equality for lower eosinophilic disease and gender equality (severe asthma has a higher prevalence in women than men)	Please see Section A.3.

Abbreviations: EOS, eosinophil; exacs, exacerbations; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL-5, interleukin 5; mOCS, maintenance oral corticosteroid treatment; NA, not applicable; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid.

A.6 Clinical effectiveness evidence – B.2.2 (page 46), B.2.3 (page 49)

The pivotal evidence for tezepelumab in the treatment of severe asthma comes from three randomised controlled trials (RCTs), summarised in Table 3:

- PATHWAY (NCT02054130), a Phase 2, multicentre, global, dose-ranging, double-blind, randomised, parallel-arm, placebo-controlled study (16, 17)

- NAVIGATOR (NCT03347279), a Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study (18-20)
- SOURCE (NCT03406078), a Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study (21)

Table 3: Clinical effectiveness evidence – B.2.3.1 (pages 50–59)

Study title	NCT02054130 (PATHWAY)† (16, 17)	NCT03347279 (NAVIGATOR) (18-20)	NCT03406078 (SOURCE) (21)
Study design	Phase 2, multicentre, multinational, dose-ranging, double-blind, randomised, parallel-arm, placebo-controlled study	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study
Population	Adults (aged 18–75 years) with physician-diagnosed asthma for ≥12 months, on a physician-prescribed asthma controller regimen with medium- or high-dose ICS plus LABA for ≥6 months, an ACQ-6 score ≥1.5 at screening, and ≥2 asthma exacerbation events or ≥1 severe asthma exacerbation resulting in hospitalisation within the prior 12 months	Adolescents and adults (aged 12–80) with physician-diagnosed asthma for ≥12 months, documented treatment with either medium- or high-dose ICS for ≥3 months, use of additional asthma controller medications for ≥3 months, ACQ-6 score ≥1.5, and ≥2 asthma exacerbation events within the prior 12 months	Adults (aged 18–80 years with physician-diagnosed asthma for ≥12 months, physician-prescribed medium- or high-dose ICS as per GINA guidelines for ≥12 months, physician-prescribed LABA and high-dose ICS for ≥3 months, OCS for asthma for ≥6 months and a stable dose of between ≥7.5 and ≤30 mg (prednisone or prednisolone), ≥1 asthma exacerbation event within the prior 12 months
Intervention(s)	In addition to standard of care: • Tezepelumab 70 mg SC Q4W (N=138) • Tezepelumab 210 mg SC Q4W (N=137) • Tezepelumab 280 mg SC Q2W (N=137)	Tezepelumab 210 mg SC Q4W in addition to standard of care (N=528)	Tezepelumab 210 mg SC Q4W plus ICS/LABA and OCS (N=74) in addition to standard of care
Comparator(s)	Placebo SC Q2W (n=138) in addition to standard of care	Placebo SC Q4W in addition to standard of care (N=531)	Placebo SC Q4W plus ICS/LABA and OCS (N=76) in addition to standard of care:
Outcomes specified in the decision problem	Asthma control: • **ACQ-6**, Total Daily Asthma Symptom Score, Global Asthma Symptom Items, night-time awakenings requiring rescue medication Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation: • **AAER** (exacerbation = requiring SCS/OCS burst, ER visit, or hospitalisation)		Asthma control: • **ACQ-6**, night-time awakenings requiring rescue medication Incidence of clinically significant exacerbations, including those that require

Study title	**NCT02054130 (PATHWAY)[†]** **(16, 17)**	**NCT03347279 (NAVIGATOR)** **(18-20)**	**NCT03406078 (SOURCE)** **(21)**
	Use of oral corticosteroids: • **Rescue medication**, **maintenance medication** Patient and clinician evaluation of response: • Total Daily Asthma Symptom Score, FeNO, ASD, CGI-C, PGI-S Lung function: • FEV$_1$, FEF$_{25–75\%}$, home PEF Adverse effects of treatment/mortality: • AEs Time to discontinuation: • Duration of study/AEs Health-related quality of life: **EQ-5D-5L**, AQLQ(S)+12, SGRQ, WPAI+CIQ		unscheduled contact with healthcare professionals or hospitalisation: • **AAER** (exacerbation = requiring SCS/OCS burst, ER visit, or hospitalisation) Use of oral corticosteroids: • **Rescue medication** • **Proportion of subjects with 100% reduction in daily OCS at Week 4** • **Proportion of subjects with daily OCS dose ≤5 mg at Week 48** • **Proportion of subjections with ≥50% reduction from baseline in daily OCS dose at Week 48** Patient and clinician evaluation of response: • FeNO, ASD, peripheral blood eosinophils, and total IgE Lung function: • FEV$_1$, FEF$_{25–75\%}$, home PEF Adverse effects of treatment/mortality: • AEs Time to discontinuation: • Duration of study/AEs Health-related quality of life: • **EQ-5D-5L**, AQLQ(S)+12, SGRQ, WPAI+CIQ

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AE, adverse event; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; CGI-I, Clinician Global Impression of Change; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; ER, emergency room; FEV$_1$, forced expiratory volume in the first second; FEF$_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NMA, network meta-analysis; OCS, oral corticosteroid; PEF, peak expiratory flow; PGI-S, Patient Global Impression of Severity; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SC, subcutaneous; SCS, systemic corticosteroid; SGRQ, St George's Respiratory Questionnaire; WPAI-CIQ, Work Productivity

and Activity Impairment Questionnaire and Classroom Impairment Questionnaire.
† PATHWAY informs the economic model indirectly via the NMA.

A.7 Key results of the clinical effectiveness evidence

A.7.1 Annualised asthma exacerbation rate (AAER) – B.2.6.1.1 (page 101), B.2.6.2.1 (page 103), B.2.6.3.2 (page 116)

- PATHWAY: Tezepelumab 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W treatment resulted in statistically significant reductions of 62, 71, and 66%, respectively, in the rate of exacerbations over 52 weeks compared with placebo (all p<0.001).
- NAVIGATOR: Tezepelumab 210 mg Q4W treatment resulted in a clinically meaningful and statistically significant 56% reduction in the rate of asthma exacerbations over 52 weeks compared with placebo (p<0.001).
- SOURCE: Treatment with tezepelumab reduced the rate of exacerbations over 48 weeks by a clinically meaningful 31% compared with placebo (p=0.111), despite subjects also reducing their long-term OCS use over this time frame.
- Tezepelumab was also shown to reduce the rate of exacerbations resulting in hospitalisations or ER visits. In PATHWAY, exacerbations resulting in hospitalisations or ER visits were reduced by 85% in the tezepelumab 210 mg arm versus placebo (p=0.017). In NAVIGATOR, the reduction was 79% (nominal p<0.001), and in SOURCE, the reduction was 41% (p=0.361).

A.7.2 Categorised percent reduction in daily OCS dose while not losing asthma control – B.2.6.3.1 (page 113)

- SOURCE did not meet its primary endpoint (categorised percent reduction in daily OCS dose while not losing asthma control), but a numerical improvement in the odds of achieving a categorical reduction in OCS dose was observed with tezepelumab 210 mg Q4W treatment versus placebo, with a cumulative OR of 1.28 (95% CI: 0.69, 2.35, p=0.434). Results are contextualised in Section A.9.

A.7.3 Asthma control and symptoms – Appendix L, B.2.6.2.3 (page 104), B.2.6.2.5 (page 108), B.2.6.3.3 (page 117)

- In all three pivotal trials, tezepelumab treatment resulted in greater improvements from baseline in Asthma Control Questionnaire 6-item (ACQ-6) than placebo, with 86.25%, 76.9%, and 65.2% of tezepelumab-treated subjects achieving clinically meaningful improvements in ACQ-6 scores in the NAVIGATOR (statistically greater improvement compared with placebo, $p<0.001$), PATHWAY, and SOURCE trials, respectively. These improvements are indicative of a reduction in activity limitation and interference with daily life caused by severe, uncontrolled asthma.
- In each trial, improvements in ACQ-6 scores were rapid, being observed at the first timepoint in which they were recorded, and sustained, lasting to the end of the treatment period.
- Asthma Symptom Diary (ASD) scores also improved with tezepelumab treatment. In NAVIGATOR, treatment with tezepelumab resulted in a clinically meaningful improvement from baseline in the weekly mean total ASD score that was statistically significant compared with placebo at Week 52 (LS mean change from baseline for tezepelumab –0.70 versus placebo –0.59; LS mean difference –0.11 [95% CI –0.19, –0.04]; $p=0.004$). Onset of improvement in ASD was seen as early as Week 2 and was maintained to Week 52. Improvements in ASD were also observed in SOURCE, suggesting that tezepelumab treatment is likely to result in improvements in asthma symptoms that are otherwise impediments to day-to-day living, sleeping, and physical activity.

A.7.4 Lung function – Appendix L, B.2.6.2.2 (page 103), Appendix N

- Tezepelumab treatment resulted in statistically significant and clinically meaningful improvements in lung function (pre-BD FEV_1) versus placebo in all three RCTs, with improvements observed at the first post-baseline time point assessed (2 weeks for NAVIGATOR and 4 weeks for PATHWAY and SOURCE) and sustained for the treatment duration.

A.7.5 Quality of life – Appendix L, B.2.6.2.4 (page 106), B.2.6.2.6 (page 110), B.2.6.3.3 (page 117)

- Tezepelumab treatment resulted in clinically meaningful improvements from baseline in quality of life, including the AQLQ[S]+12, [redacted], compared with placebo in the PATHWAY, NAVIGATOR and SOURCE trials.
- In SOURCE, tezepelumab-treated subjects had a greater improvement in [redacted] compared with placebo despite the reduction in OCS dose ([redacted]).

A.7.6 Safety – B.2.10 (page 179)

- Across the NAVIGATOR, PATHWAY, and SOURCE trials, tezepelumab was well tolerated in patients with severe asthma and demonstrated a favourable risk-benefit profile.
- The safety profile of tezepelumab was similar to that of optimised standard of care, with commonly reported AEs such as nasopharyngitis and headache occurring at comparable rates in both treatment arms.
- Across the clinical trial programme there were no anaphylactic or serious allergic reactions considered causally related to tezepelumab by the investigator.
- Tezepelumab was associated with low discontinuation rates in patients with severe, uncontrolled asthma across phenotypes and irrespective of biomarkers.

A.8 Evidence synthesis – B.2.9 (page 151)

Because the economic model enrolled a stratified patient population, NMA outcomes, where possible, were also assessed in the following subgroups of patients: High blood EOS level (≥150 cells/µL, ≥300 cells/µL), low blood EOS level (<150 cells/µL, <300 cells/µL), ≥3 exacerbations in the prior 12 months, high FeNO level (≥25 ppb, ≥50 ppb), allergic asthma. The following specific NMAs were used to inform the model:

- Reduction in AAER:

  - High blood EOS level (≥300 cells/µL) subgroup (anti-IL-5 eligible population [benralizumab, mepolizumab]) – Section B.2.9.2.1.2 (page 158)
  - Low blood EOS level (<300 cells/µL) subgroup (dupilumab eligible population) – Section B.2.9.2.1.4 (page 160)
  - Allergic asthma subgroup (omalizumab eligible population) – Section B.2.9.2.1.8 (page 164)
- Reduction in AAERs leading to hospitalisations ITT population: – Section B.2.9.2.2 (page 165)
- mOCS reduction – High blood EOS level (≥300 cells/µL) subgroup (anti-IL-5 eligible population [benralizumab, mepolizumab]) – Section B.2.9.2.3.1 (page 168)

Overall, in each NMA listed above, with the exception of the reduction in AAER high blood EOS level (≥300 cells/µL) subgroup (in which dupilumab 300 mg – which is not a NICE-recommended dose – was the highest ranked treatment), tezepelumab was the numerically favoured treatment.

A.9 Key clinical issues – B.2.13.2 (page 193)

- Results from the SOURCE trial favoured tezepelumab over placebo, but the primary endpoint (categorised percent reduction in the daily OCS dose without loss of asthma control at Week 48) did not reach statistical significance and hence was not met. The reasons for this are believed to be:
  - The strong placebo response rate seen in SOURCE, which could have played a role in the observed OCS dose reduction results.
  - The proportion of patients in the placebo arm with successful categorised percent reduction in OCS dose – which was substantially higher than was anticipated based on previous OCS-reduction studies with biologics (22).
  - SOURCE had a longer OCS dose reduction period (36 weeks versus 16-20 weeks in other studies) giving all patients, including those receiving placebo, a greater opportunity to down-titrate their daily OCS dose to 0 mg compared with other studies, in turn contributing to the higher observed placebo response rate in SOURCE.

  - Protocol guidance in SOURCE strongly encouraged investigators to continue OCS down-titration despite periodic worsening of asthma. This was investigated further via a post hoc analysis in which the duration of the OCS reduction phase was reduced from 36 weeks to 20 weeks and further OCS reduction was not permitted in subjects who experienced one or two exacerbations (or in patients who did not meet the asthma control criteria after randomisation). This analysis resulted in a nominally statistically significantly higher odds of subjects achieving a 90–100% reduction in OCS compared with placebo (cumulative OR: 2.16; 95% CI: 1.20, 3.89; nominal p=0.010)
- The above assumptions as to why SOURCE did not meet statistical significance on the primary endpoint have been validated with UK clinicians. In addition to the trial design, clinicians also believe that patient recruitment/selection may have had a part to play. Clinicians highlighted that there are no UK centres included in the trial and that the majority were from the South American region where clinical practice allows quicker dose escalation and treatment switching leading to a greater placebo response (23). Despite these limitations, clinicians still perceive there to be value in the data that SOURCE produced as there were subgroups with significant responses despite seeing a larger placebo effect than hoped. As a result, in clinical practice, clinicians would expect to see OCS sparing as result of tezepelumab treatment based off experience with current biologics and tezepelumab's mode of action targeting higher up in the inflammatory cascade and their understanding of severe asthma immunology in relation to the mode of action of tezepelumab (23).
- In the NMA for the reduction in AAER leading to hospitalisations outcome, data were only available for the ITT population, whereas it would have been preferrable to have been able to mirror the subgroup approach as used for the reduction in AAER outcome.
- No data were available from the NMA to inform the relative effects of omalizumab in reducing mOCS. An assumption of equivalence between tezepelumab and omalizumab was therefore required in the economic model

A.10 Overview of the economic analysis – B.3.2.2.1 (page 218)

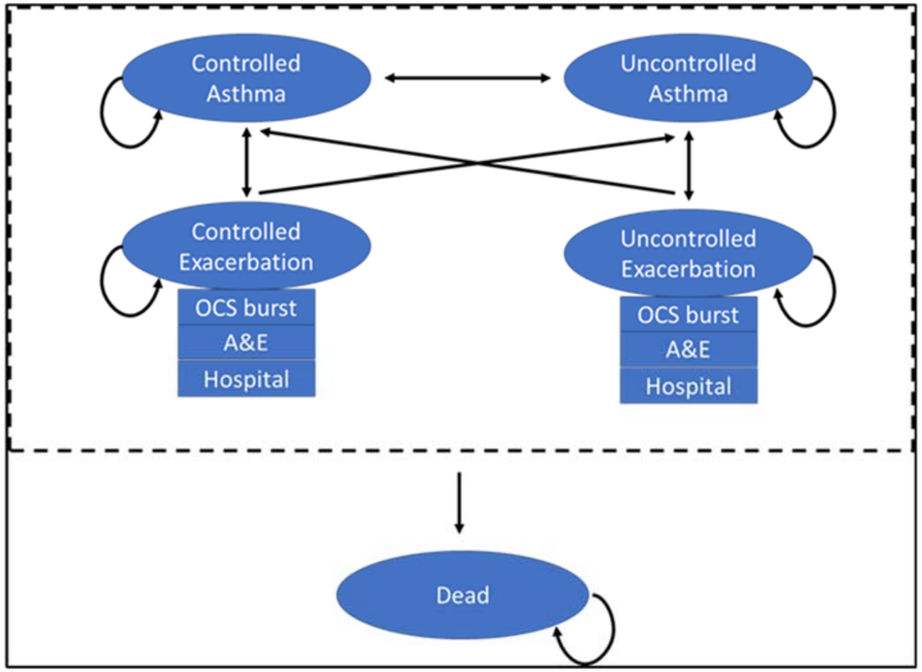
The economic evaluation assessed the cost-effectiveness of tezepelumab as an add-on to SoC and (in totality) considered patients with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year, or who are on mOCS. The modelled patient population was stratified into subgroups so as to take account of NICE's recommendations in appraisals conducted for biologic treatments in this disease area (see Table 97 in Form B).

The base case model was a 5-state Markov cohort model with 4-week cycles considered over a lifetime (60 year) horizon. Definitions of health states were as follows:

- Controlled asthma: ACQ-6 <1.5 without exacerbation
- Uncontrolled asthma: ACQ-6 ≥1.5 without exacerbation
- Exacerbation: Worsening of asthma symptoms which causes one of three composite events:
  - Burst of OCS for at least three consecutive days
  - An emergency room or A&E visit
  - Hospitalisation
- Exacerbations in the model were defined as either controlled or uncontrolled based on asthma status prior to the exacerbation
- Dead: Includes asthma-related mortality and all-cause (non-asthma-related) mortality

A schematic of the model structure is presented in Figure 3.

Figure 3: Model structure – B.3.2 (page 219)



Abbreviations: A&E, Accident and Emergency; OCS, oral corticosteroid.

A.11 Incorporating clinical evidence into the model

A.11.1 Treatment efficacy – B.3.3.2 (page 226)

Treatment efficacy was captured in the model through cost offsets and QALY gains. The main treatment benefits associated with tezepelumab versus SoC included: reduction in the rate of exacerbations, reduction in the proportion of exacerbations leading to hospitalisation, reduction in ACQ-6 score, and OCS sparing.

A.11.2 Consequences of OCS use – B.3.3.3 (page 248)

OCS-related adverse events were modelled in terms of their impact on both costs and QoL. In order to quantify the impact of OCS use, AstraZeneca commissioned a matched historical cohort study using the OPCRD, and the Clinical Practice Research Datalink (CPRD) database (AstraZeneca data on file 2017). Modelled adverse events associated with OCS use and their annual probabilities are summarised in Table 121 (page 248) of Form B. Annual probabilities were converted to 4-week probabilities in the model.

A.11.3 Mortality – B.3.3.4 (page 250)

Mortality was captured in the model as asthma-specific mortality and all-cause mortality. Asthma-specific mortality occurred as a result of exacerbation, with the risk varying according to the type of exacerbation and the age of the patient. Asthma-specific mortality was sourced using ONS data for ICD-10 codes J45-J46, stratified by age and gender. All-cause mortality formed the baseline mortality rate in the model and was taken from the latest UK life tables, stratified by age and gender (24). Exacerbation-specific mortality used input values from three UK studies: Watson 2007 (25), Roberts 2013 (26), and the 2014 National Review of Asthma Deaths (NRAD) report (27).

The methods used in the model for calculating mortality aligned with those described in the NICE submission for benralizumab (28) but with exacerbation data derived from NAVIGATOR and SOURCE. The approach assumed that asthma-related mortality could only occur following an exacerbation.

A.12 Key model assumptions and inputs – B.3.6.2 (page 267)

The derivation of model inputs is described in full at sections B.3.3 to B.3.5. A list of all model parameters can be found at Appendix P. Key assumptions are presented in Table 4.

Table 4: Key model assumptions

Assumption	Rationale
NMA results: Where no data were sourced for individual outcomes in the ITT population, inputs were assumed to be equivalent to tezepelumab	No data were available to inform the relative effects of omalizumab in reducing mOCS
NMA results: The same values for exacerbation rate ratios were applied both pre- and post-response assessment	No data were available to support stratifying by response period
NMA results: Hospitalised exacerbation rate of ITT population used in all subpopulations	No hospitalised exacerbation rate was detailed for any subpopulation, therefore ITT had to be used
No waning treatment effect is captured in the model	No evidence to suggest there is a loss of effect in the long-term
The relative probability of discontinuing mOCS was not found in the NMA and therefore was assumed to be equal to a >90% probability	The best assumption that could be made with the available data
[redacted]	[redacted]
Patients could not transfer from controlled asthma to uncontrolled exacerbation. If this were the case, i.e. a drop in ACQ score simultaneously with an exacerbation, the patient would have entered controlled exacerbation (i.e. any change in ACQ score was assumed to be due to the exacerbation itself where an exacerbation was ongoing)	Allowed for the impact of exacerbations related to prior ACQ-6 score to be explored. Removing this assumption would have meant some effect of tezepelumab may not be explicitly captured

Abbreviations: ACQ, Asthma Control Questionnaire; ACQ-6, Asthma Control Questionnaire 6-item; ITT, intent-to-treat; mOCS, maintenance oral corticosteroid treatment; NMA, network meta-analysis.

A.13 Base case ICER (deterministic) – B.3.7.1 (page 267)

The base case considered tezepelumab as an add-on to SoC treatment and (in totality) in patients with severe asthma despite high dose ICS and an additional controller, who either experienced three or more exacerbations in the prior year, or who were receiving mOCS. The modelled patient populations were stratified into subgroups to take account of NICE's previous recommendations in appraisals conducted for biologic treatments in this disease area. By demonstrating cost-effectiveness across all subgroups, tezepelumab can be considered cost-effective in all patients with severe uncontrolled asthma despite high dose ICS and an additional controller, who have 3 or more exacerbations in the prior year or who are on mOCS, and irrespective of biomarker values.

Note that the model considered tezepelumab at its confidential PAS price whereas the comparator biologics were included using their respective list prices.

Table 5: 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]	£1,039,106	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.

Table 6: Base case results (dupilumab 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]	-	-	-		
Dupilumab + 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.

Table 7: Base case results (omalizumab 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]	-	-	-		
Omalizumab + 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.

Table 8: 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)	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,968	£29,968

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.

A.14 Probabilistic sensitivity analysis – B.3.8.1 (page 277)

The results of PSA were found to be highly congruent with the deterministic base case results and showed that, in the anti-IL-5 eligible, dupilumab eligible, and omalizumab eligible cohorts, tezepelumab remained the dominant treatment choice. In the non-bio eligible cohort, the ICER decreased slightly from £29,968 to £29,962. At a cost-effectiveness threshold of £20,000 per QALY, tezepelumab was cost-effective in [redacted] of simulations, increasing to [redacted] at a cost-effectiveness threshold of £30,000 per QALY.

Table 9: 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]	£519,074	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.

Table 10: Probabilistic results (dupilumab 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]	-	-	-		
Dupilumab + 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.

Table 11: Probabilistic results (omalizumab 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]	-	-	-		
Omalizumab + 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.

Table 12: 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)	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,962	£29,962

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.

A.15 Key sensitivity and scenario analyses – B.3.8.2 (page 281) and B.3.8.4 (page 292)

Figure 4: Tornado diagrams

[redacted]

[redacted]

[redacted]

Table 13: Key scenario analyses

Scenario and cross reference	Brief rationale	Impact on base-case ICER
Base case (for reference)		See Section A.13
Alternative exacerbation-related mortality – B.3.8.3.1 (page 293)	To explore the impact of calibrating all-cause mortality in the model to 3-year mortality as reported in a real world study of severe asthma patients. A further scenario calibrated the model to the reported real world mortality + 50%, in recognition of the fact that the target population for this appraisal exhibits greater disease burden than the population considered in the real world study	**Non-bio eligible (3+ exacs or mOCS)** Tezepelumab (vs SoC): Model calibrated to real world study mortality: • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): £21,091 Model calibrated to real world study mortality + 50%: • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): £16,793
Using alternative sources for patient baseline characteristics – B.3.8.3.2 (page 296)	In the model base case, Jackson 2021 (29) was used to inform the modelled patient baseline characteristics as this study was based on patients within the UK Severe Asthma Registry. However, it does deviate from the population characteristics reported in NAVIGATOR and SOURCE. A scenario analysis was therefore conducted utilising the patient characteristics from the NAVIGATOR and SOURCE studies.	**Anti-IL-5 eligible** Mepolizumab (vs tezepelumab): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated Benralizumab (vs tezepelumab): • Incremental cost: [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated **Dupilumab eligible** Dupilumab (vs tezepelumab): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated

Scenario and cross reference	Brief rationale	Impact on base-case ICER
		Omalizumab eligible Omalizumab (vs tezepelumab): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated **Non-bio eligible (3+ exacs or mOCS)** Tezepelumab (vs SoC): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): £30,937
Alternative comparative exacerbation rates – B.3.8.3.4 (page 300)	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 (Section B.2.9.2.1.5). Data were only available for the comparison between tezepelumab + SoC and benralizumab + SoC. Mepolizumab + SoC was therefore conservatively assumed to be equivalent to benralizumab + SoC, consistent with the approach taken in the benralizumab submission (28). For dupilumab, three alternative NMA subgroups were used to inform this scenario: 1. FeNO High: ≥25 ppb subgroup NMA data (Section B.2.9.2.1.6) 2. ≥3 Exacerbations in last 12 months subgroup NMA data (Section B.2.9.2.1.5) 3. EOS High: ≥150 cells/µL subgroup NMA data (Section B.2.9.2.1.1)	**Anti-IL-5 eligible** Mepolizumab (vs tezepelumab): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated Benralizumab (vs tezepelumab): • Incremental cost: [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated **Dupilumab eligible (scenario 1)** Dupilumab (vs tezepelumab): • Incremental cost [redacted] • Incremental QALY: [redacted] • ICER versus baseline (£/QALY): Dominated **Dupilumab eligible (scenario 2)** Dupilumab (vs tezepelumab):

Scenario and cross reference	Brief rationale	Impact on base-case ICER
		- Incremental cost [redacted] - Incremental QALY: [redacted] - ICER versus baseline (£/QALY): Dominated **Dupilumab eligible (scenario 3)** Dupilumab (vs tezepelumab): - Incremental cost [redacted] - Incremental QALY: [redacted] - ICER versus baseline (£/QALY): Dominated

Abbreviations: EOS, eosinophil; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; IL, interleukin; NMA, network meta-analysis; ppb, parts per billion; QALY, quality-adjusted life year; SoC, standard of care.

A.16 Innovation – B.2.12 (page 190)

Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of TSLP. By blocking the activity of TSLP at the top of the airway inflammatory pathway, tezepelumab reduces the initiation and persistence of multiple downstream inflammatory responses (17, 30, 31). Thus, the effects of tezepelumab are potentially broader than those of current biologic therapies for severe asthma, which are targeted to single or downstream inflammatory pathways (32). This novel mechanism of action allows tezepelumab to deliver efficacy for severe asthma patients regardless of biomarkers or phenotype.

Tezepelumab is the only biologic proven to consistently reduce the rate of asthma exacerbations in severe asthma patients across phenotypes and irrespective of baseline levels of blood EOS, FeNO, or specific IgE (17, 19) . Furthermore, tezepelumab has also been shown to reduce the levels of FeNO, IL-4, IL-5, IL-13 and IgE. In clinical trials, tezepelumab significantly reduced the rate of asthma exacerbations by up to 71% versus SoC across all severe, uncontrolled asthma patients regardless of phenotype and irrespective of biomarker levels (17, 19). The NMA conveyed a numerical advantage for tezepelumab versus NICE recommended biologics for exacerbations and hospitalised exacerbations. Tezepelumab is the first and only biologic that has demonstrated statistically significant reductions in annual exacerbation rates among patients with low EOS counts (<300 cells/µL and <150 cells/µL).

Tezepelumab is currently the only biologic to demonstrate a reduction in airway hyperresponsiveness which is a clinically important and relevant outcome. The CASCADE study demonstrated the effect of tezepelumab on airway tissue inflammatory cells, and the broader mechanisms by which tezepelumab improves clinical asthma outcomes. Tezepelumab is the only biologic currently to show a reduction in airway hyperresponsiveness to mannitol, indicating that the TSLP blockade may have additional benefits in asthma beyond reducing T2 airway inflammation (33). Feedback from UK clinicians (n=7) highlighted how data on airway hyperresponsiveness is an area of clinical differentiation for tezepelumab (23).

Tezepelumab potentially simplifies the treatment of severe, uncontrolled asthma patients and will provide an additional treatment option for patients who are currently eligible for biologic treatment and provide access to a biologic treatment for some patients who are currently ineligible.

A.17 Budget impact

Table 14: Expected five-year budget impact summary (Tezepelumab list price) – Budget Impact Submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population	92,392	94,055	95,748	97,471	99,226
Eligible population using a biologic (world without tezepelumab)	11,449	12,250	13,108	14,026	15,007
Eligible population using a biologic (world with tezepelumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of biologics world without tezepelumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use cost world without tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of biologic treatments world without tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of biologics world with tezepelumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use cost world with tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of biologic treatment world with tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Cost of biologics includes SoC cost for all therapies, and administration and monitoring cost (applicable to Reslizumab).
Abbreviations: SoC, standard of care.

Table 15: Expected five-year budget impact summary (Tezepelumab net price) – Budget Impact Submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population	92,392	94,055	95,748	97,471	99,226
Eligible population using a biologic (world without tezepelumab)	11,449	12,250	13,108	14,026	15,007
Eligible population using a biologic (world with tezepelumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of biologics world without tezepelumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use cost world without tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of biologic treatments world without tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of biologics world with tezepelumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use cost world with tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of biologic treatment world with tezepelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Cost of biologics includes SoC cost for all therapies, and administration and monitoring cost (applicable to Reslizumab).
Abbreviations: SoC, standard of care.

A.18 Interpretation and conclusions of the evidence

This appraisal positions tezepelumab as a treatment for adults and adolescents 12 years and older with severe uncontrolled asthma patients despite high dose ICS and an additional controller, who have had 3 or more exacerbations in the prior year, or who are on maintenance OCS, irrespective of biomarker values. Introducing tezepelumab in this setting will provide access to a biologic treatment for some patients who are currently ineligible and provide an additional treatment option for patients who are currently eligible for biologic treatment.

This submission presents the compelling evidence base for tezepelumab and demonstrates that the use of tezepelumab in this indication represents a clinically relevant and cost-effective use of National Health Service (NHS) resources with a base case incremental cost-effectiveness ratio (ICER) below that of NICE's standard willingness to pay threshold regardless of comparator. Having access to tezepelumab in the 3 or more exacerbations or mOCS population will enable more patients to have access to biologic therapy and importantly help to simplify the treatment landscape.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tezepelumab for treating severe asthma (ID3910)

Clarification questions

June 2022

File name	**Version**	**Contains confidential information**	**Date**
ID3910_Teze ERG clarification questions_Company response [CIC redacted]	V1.0	Yes	28/06/2022

Section A: Clarification on effectiveness data

Clarification of search methods

A1. Please provide the rationale for using different search terms for the population for the clinical effectiveness searches (reported in D.1.1.3-D.1.1.4) to those applied in the SLRs for cost-effectiveness, health related quality of life and cost & resource use (G.1.1.1-G.1.1.2; H.1.1.1-H.1.1.2; I.1.1.1.-I.1.1.2). In the clinical effectiveness SLR, controlled vocabulary terms for asthma have not been exploded to include narrower relevant terms in the hierarchy (for e.g. the EMTREE term for asthma/ has not been exploded, and the relevant term for eosinophilic asthma/ not included in the Embase search strategy.)

The clinical effectiveness and non-clinical SLRs were conducted as two different workstreams and therefore there were slight differences used in the syntax employed. In the clinical SLR, the population was defined as severe or uncontrolled asthma (GINA step 4 and 5). The other subcategories available in the MEDLINE MeSH tree were considered not applicable because studies relevant to our population would already be comprehensively captured by the other terms.

The search protocol was designed based on MEDLINE and thereafter translated into Embase in a similar fashion as the MEDLINE design. Therefore, in Embase, we employed an analogous strategy by selecting the highest-level term for asthma.

Additionally, the search included keyword vocabulary that aimed to capture all relevant studies therefore adding the eosinophilic asthma/ term or exploding the asthma/ term would not have identified additional eligible studies. To confirm this and in response to the question above, we ran a new search that included appropriate additional terms for eosinophilic asthma which yielded no additional relevant studies. The search strategy and results have been provided below.

AZ_Teze_Clarification%20search.docx

AZ_Teze_additional%20search%20results.xl

A2. Were specific searches were conducted to identify adverse reaction data for tezepelumab (in addition to searches for RCTs in the clinical effectiveness SLR).

At the time the search for the clinical SLR was ran, tezepelumab was not licensed in any country, so there were no real-world data available. Other than the clinical trials there have been no studies which have sought to estimate the rate of adverse events with tezepelumab, therefore the searches were not designed to capture this.

Clarification of other clinical SLR methods

A3. All three pivotal trials were designated as 'publications identified from additional sources' (Table 3, Appendix D). Please provide clarification on the methods used to identify these studies (i.e. which SLR processes were these studies identified through, and if not identified through the SLR, please clarify the processes used to identify these).

At the time the clinical SLR was run, the full details of the three tezepelumab clinical trials were not available in the public domain and therefore in order to ensure that all data were captured, the CSRs were used to report the pivotal trials. The primary publication for PATHWAY (Corren 2017) and several supporting conference abstracts were identified through the database and grey literature searches, respectively. Similarly, conference abstracts related to SOURCE and NAVIGATOR were identified through grey literature searching.

A4. Please provide details of the methods of data extraction for the SLR of clinical effectiveness.

Data from the included clinical trials were collected using a standardised data extraction form in Microsoft® Excel (Microsoft Corporation, Seattle, US). The data extraction form was piloted using a sample of key citations and updated accordingly prior to implementation. Data extraction was performed by a single reviewer and was independently assessed for accuracy and completeness by a second reviewer. Disagreements were resolved by a third independent reviewer, as necessary. The specific data elements that were captured included: general study information (e.g., reference identification, trial name, National Clinical Trial [NCT] number, author, publication date), study characteristics (e.g., study design, RCT phase, blinding, location, analysis population), treatment design details (e.g., interventions, dosing regimen, route of administration, treatment duration, length of follow-up), baseline population characteristics (e.g., sample size, age, sex, race, weight, disease severity, treatment history), and efficacy and safety endpoints (e.g., definition of endpoints, timeframe of assessments, results). Values of interest that were reported in figures but not text were estimated using the DigitizeIt software.

A5. It appears that the CRD guidance was used to perform quality appraisal for the three tezepelumab trials; please either provide justification for not using a standardized risk of bias tool (e.g. RoB2) or provide assessments using such a tool.

We appreciate that there are a number of validated tools that can be used to assess the quality of clinical studies. The quality assessment checklist adapted from the CRD's guidance for undertaking reviews in healthcare which was used to assess the three tezepelumab RCTs is the recommended tool for assessing parallel group RCTs in Section 2.5 of the NICE user guide company evidence submission template (updated 10th February 2022).[1] Therefore, it was deemed appropriate this was the checklist used to assess the bias of the pivotal trials. For completeness we have also provided an assessment of the three pivotal tezepelumab RCTs using the NICE Quality appraisal checklist for quantitative intervention studies ('adapted GATE checklist' used to assess the studies included in the NMA) in Table 1. The findings concur with those reported using the CRD checklist in section B.2.5 of the submission document, indicating that the trials were well conducted and methodologically robust.

Table 1: Summary of an alternative quality assessment for the tezepelumab trials[2]

Questions	NAVIGATOR (2020); NCT03347279	SOURCE (2020); NCT03406078	PATHWAY (2017); NCT02054130
Section 1: Population			
1.1 Is the source population or source area well described?	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++

Questions	NAVIGATOR (2020); NCT03347279	SOURCE (2020); NCT03406078	PATHWAY (2017); NCT02054130
Section 2: Method of allocation to intervention (or comparison)*			
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++
2.3 Was the allocation concealed?	++	NA	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	++	+	+
2.6 Was contamination acceptably low?	+	+	++
2.7 Were other interventions similar in both groups?	++	+	++
2.8 Were all participants accounted for at study conclusion?	++	++	++
2.9.1 Did the setting reflect usual North American practice?	++	++	++
2.9.2 Did the setting reflect usual EU practice?	++	++	++
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NA
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	+	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	+	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA
Section 3: Outcomes			
3.1 Were outcome measures reliable?	++	++	++
3.2 Were all outcome measurements complete?	++	++	++
3.3 Were all important outcomes assessed?	++	++	++
3.4 Were outcomes relevant?	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++
3.6 Was follow-up time meaningful?	++	++	++
Section 4: Analyses			
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++
4.2 Was ITT analysis conducted?	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	+
4.4 Were the estimates of effect size given or calculable?	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	+	-

Questions	NAVIGATOR (2020); NCT03347279	SOURCE (2020); NCT03406078	PATHWAY (2017); NCT02054130
Section 5: Summary			
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.
*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

A6. Please also provide justification for using different processes for assessing ROB in the three tezepelumab trials and the other included trials (i.e. those included in the NMAs)

As discussed in the response to question A5, there are a number of validated checklists which can be used to assess the degree of bias in clinical studies. Both of the checklists used for the submission are validated and examine the same criteria for assessing the risk of bias (e.g. method of randomisation, allocation concealment, use of ITT analysis etc) and would therefore identify any issues with the robustness of the trials with regard to design and/or execution:

- CRD checklist used to assess three pivotal tezepelumab RCTs: recommended in section 2.5 of the NICE STA user guide for company evidence submission template[1]
- Adapted-GATE checklist used to assess studies in the NMA: recommended in Appendix F of ‘Methods for the development of NICE public health guidance’ document[2]

Different tools were used to assess bias as these were two separate workstreams. The assessment of the RCTs included in the NMA was conducted as part of the clinical SLR, whereas assessment of the pivotal trials using the CRD checklist was performed as part of Form B being drafted.

Clarification on the pivotal trials

A7. Geographical spread cannot be inferred from Doc B, Figures 23, 25 and 26 because broad geographical categories are used and the categories differ between trials. For each trial, please provide the number of participants recruited and treated in each country.

The number of participants recruited in total and by treatment arm in each region and country in the PATHWAY, NAVIGATOR and SOURCE trials are found in Table 2, Table 3 and Table 4. Further information (i.e., number of participants by centre) is available in the NAVIGATOR and SOURCE clinical study report (CSR) table 14.1.5 and 14.1.4 respectively.

Table 2: PATHWAY, subject recruitment and treatment by region and country

Region	Country	Number (%) of subjects		
		Tezepelumab 210 mg Q4W (N=137)	**Placebo (N=138)**	**Total (N=275)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Source: Internal AZ data on file.
Abbreviations: Q4W; every 4 weeks.

Table 3: NAVIGATOR, subject recruitment and treatment by region and country

Region	Country	Number (%) of subjects		
		Tezepelumab 210 mg Q4W (N=528)	**Placebo (N=531)**	**Total (N=1059)**
Asia Pacific	South Korea	54 (10.2)	72 (13.6)	126 (11.9)
	Japan	58 (11.0)	39 (7.3)	97 (9.2)
	Vietnam	8 (1.5)	12 (2.3)	20 (1.9)
	Taiwan	5 (0.9)	4 (0.8)	9 (0.8)
	Total Asia Pacific	125 (23.7)	127 (23.9)	252 (23.8)
North America	USA	92 (17.4)	94 (17.7)	186 (17.6)
	Canada	19 (3.6)	17 (3.2)	36 (3.4)
	Total North America	111 (21.0)	111 (20.9)	222 (21.0)
South America	Brazil	47 (8.9)	46 (8.7)	93 (8.8)
	Argentina	40 (7.6)	41 (7.7)	81 (7.6)
	Total South America	87 (16.5)	87 (16.4)	174 (16.4)
Western Europe plus Australia	Germany	56 (10.6)	47 (8.9)	103 (9.7)
	France	20 (3.8)	21 (4.0)	41 (3.9)
	Australia	8 (1.5)	11 (2.1)	19 (1.8)
	Austria	2 (0.4)	6 (1.1)	8 (0.8)
	Total Western Europe plus Australia	86 (16.3)	85 (16.0)	171 (16.1)
Rest of the world	South Africa	51 (9.7)	58 (10.9)	109 (10.3)
	Israel	25 (4.7)	22 (4.1)	47 (4.4)
	Saudi Arabia	5 (0.9)	2 (0.4)	7 (0.7)
	Total Rest of the world	81 (15.3)	82 (15.4)	163 (15.4)
Central/Eastern Europe	Russia	25 (4.7)	26 (4.9)	51 (4.8)
	Ukraine	13 (2.5)	13 (2.4)	26 (2.5)
	Total Central/Eastern Europe	38 (7.2)	39 (7.3)	77 (7.3)

Source: NAVIGATOR CSR Table 14.1.5 subject recruitment by region, country and centre (full set analysis).
Abbreviations: Q4W; every 4 weeks.

Table 4: SOURCE, subject recruitment and treatment by region and country

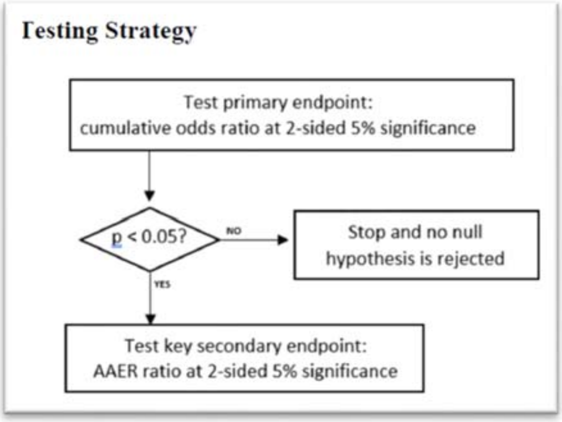
Region	Country	Number (%) of subjects		
		Tezepelumab 210 mg Q4W (N=74)	Placebo (N=76)	Total (N=150)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Source: SOURCE CSR Table 14.1.4 subject recruitment by region, country and centre (full set analysis).
Abbreviations: Q4W; every 4 weeks.

A8. The submission states that AAER in SOURCE was "not formally assessed". Please clarify what is meant by this and provide further details on how the AAER data were derived in this study (including how exacerbations were defined).

Annualised asthma exacerbation rate (AAER) ratio vs placebo was defined as a key secondary endpoint in SOURCE, with the categorised percent reduction from baseline in daily OCS at Week 52 defined as the primary endpoint. The overall Type 1 error rate was strongly controlled at the 5% level in the study using a hierarchical testing strategy to assess the primary and key secondary endpoints, as defined in Section 4.1.2 of the SOURCE Statistical Analysis Plan (SAP).[3] As the primary endpoint did not achieve statistical significance, no further testing was performed (as demonstrated in Figure 1 below from the SAP). Therefore, no formal testing of the key secondary endpoint of AAER was conducted.

Figure 1: Testing strategy for SOURCE



An asthma exacerbation is defined in the SOURCE Clinical Study Protocol,[4] Section 8.1.2, as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids. Note: Per protocol up titration of OCS dose to 1 level higher (as described in Table 9 of the CSP) is not considered an exacerbation per se.
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (as per above).
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

Further details on the derivation of the AERR for the statistical analyses can be found in Section 3.2.2.1 of the SOURCE SAP.

Clarification on the NMAs

A9. Please clarify which NMAs relied on contrast-level data (e.g. log rate ratios) and which ones relied on arm-level data.

All of the subgroup NMAs relied on contrast-level data and all the primary and sensitivity NMAs relied on arm-level data.

A10. Please provide all code files as run and all data frames as inputted for each NMA presented (primary and subgroup analyses).

All the code files and all the data frames used in each NMA are available in the embedded file below.

[redacted]

A11. Please present a table of fit statistics for each comparison of fixed and random effects NMA for each NMA presented (primary and subgroup analyses).

The NMA model fit statistics for each comparison of the fixed and random effects NMA are shown below in Table 5.

Table 5: Fixed and random effects for each NMA presented

Outcome	Analysis	Type	Total number of patients	DIC	TRD	Number of data points	SD (95% Crl)
AAER	Primary	RE	10,092	319.09	34.88	35	0.261 (0.156 to 0.478)
		FE		370.56	95.52		-
	Subgroup (≥150 blood EoS cells/µL)	FE	4,660	-7.78	6.48	8	-
		RE		-7.1	7.28		0.192 (0.008 to 3.06)
	Subgroup (≥300 blood EoS cells/µL)	RE	4,873	-3.91	13.1	14	0.195 (0.029 to 0.538
		FE		0.26	17.33		-
	Subgroup (<150 blood EoS cells/µL)	FE	1,095	3.33	7.72	6	-
		RE		1.85	6.31		0.79 (0.036 to 4.199)
	Subgroup (<300 blood EoS cells/µL)	RE	2,699	1.04	8.82	8	0.527 (0.095 to 1.89)
		FE		8.41	16.19		-
	Subgroup (≥3 exacerbations in past 12 months)	RE	1,566	-2.75	7.14	8	0.184 (0.01 to 1.322)
		FE		-2.91	7.07		-
	Subgroup (≥25 ppb FeNO level)	FE	1,684	-0.39	3.73	4	-
		RE		-0.29	3.84		0.923 (0.038 to 4.577)
	Subgroup (≥50 ppb FeNO level)	FE	696	-0.4	2.96	3	-
		RE		-0.39	3.02		2.563 (0.119 to 4.878)
	Subgroup (Allergic)	RE	5,411	-4.47	12.24	11	0.252 (0.013 to 0.900)
		FE		0.3	16.7		-
	Subgroup (Triple-positive patients)	FE	918	-1.69	2.00	2	-
		RE		-1.66	1.98		2.525 (0.117 to 4.886)
HospAAER	Primary	RE	6,965	151.89	22.26	22	0.397 (0.03 to 1.329)
		FE		152.03	25.9		-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]

Outcome	Analysis	Type	Total number of patients	DIC	TRD	Number of data points	SD (95% CrI)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ, Asthma Control Questionnaire; CrL, credible interval; DIC, deviance information criterion; EOS, eosinophil; FE, fixed effects; FeNO; fractional exhaled nitric oxide; FeV1, forced expiratory volume in first second; NMA. network meta-analysis; OCS, oral corticosteroid; ppb, parts per billion; RE, random effects; SD, standard deviation; TRD; total residual deviance.

A12. Please clarify why some subgroup analysis NMAs that are also not sensitivity analyses are described as 'adjusted' whereas others are not (e.g. Figure 42).

The inclusion of the word “Adjusted” in some subgroup analyses is an error. The analyses in Figures 36, 38, 39, 41 and 42 were not adjusted.

Section B: Clarification on cost-effectiveness data

Clarification on search methods

B1. The PRISMA flow diagram (Figure 102, Appendix G) indicates that 27 relevant records were identified after full-text screening, including 14 abstracts. Please provide citations for the 14 relevant abstracts and clarify why these were excluded?

The citations for the 14 relevant abstracts are found in Table 6. Due to limited reporting of key aspects of model methodology/structure and outcome data in publications reported as conference abstracts only, it was agreed to limit studies for detailed extraction to those reported as full publications. The citations therefore provided below were excluded as they are all abstracts only.

Table 6: List of abstract publications included in the original 2017 economic evaluation SLR but not extracted

Author	Citation	Title
Ariza JG	Value Health. 2012;15 (4):A56.	Cost-utility analysis of omalizumab compared with standard therapy in patients over twelve years old with severe asthma from the Colombian health system perspective
Bogart M	Value Health. 2015;18 (3):A174.	Cost-effectiveness of refractory asthma treatment strategies: A decision tree analysis.
Castonguay A	Value Health. 2016;19 (7):A556.	Development of a global model for the economic evaluation of a biomarker for the treatment of uncontrolled moderate to severe asthma.
Castro Cordero JA	Value Health. 2017;20 (5):A201-A2.	Economical impact of treatment with omalizumab in Costa Rican social security.
Faria R	Value Health. 2013;16 (7):A373.	Integrating the long-term health burden of oral corticosteroids in the cost-effectiveness of omalizumab.
Kolbin A	Value Health. 2016;19 (7):A555.	Pharmacoeconomic analysis of treatment of adult patients with severe uncontrolled asthma with omalizumab in Russia
Kolbin A	Value Health. 2016;19 (7):A555.	Pharmacoeconomic analysis of treatment of children with severe uncontrolled asthma with omalizumab in Russia.
Lemus-Carmona E	Value Health. 2012;15 (7):A563-A4	Cost analysis of omalizumab use in patients with severe uncontrolled asthma within the mexican public health care system.

Author	Citation	Title
Moital I	Value Health. 2016;19 (7):A555-A6.	Estimating the impact associated to the use omalizumab in the treatment of severe persistent allergic asthma in Portugal-evaluating outcomes and treatment costs using real world data from Portuguese patients.
Sonathi V	Value Health. 2014;17(7):A597-8.	Evaluation of Omalizumab Compared With Standard Therapy in the Treatment of Severe Allergic Asthma in Adult Patients in Greece: a Cost Effectiveness Analysis Based on Clinical Trial and Real-World Data.
Suzuki C	Value Health. 2013;16 (3):A234.	Economic evaluation of omalizumab ADD-on therapy in patients with uncontrolled severe allergic asthma from the private health care system perspective in Brazil.
Suzuki C	Revista Brasileira de Medicina. 2015;72(1-2).	Economic evaluation of omalizumab add-on therapy in patients with uncontrolled severe allergic asthma from the perspective of Unified Health System in Brazil. [Portuguese].
Suzuki C	Value Health. 2012;15 (7):A564.	Economic evaluation of omalizumab in patients with uncontrolled severe allergic asthma from the public payer perspective in Brazil.
Zafari Z	American Journal of Respiratory and Critical Care Medicine 2015;191(no pagination).	Cost-effectiveness of tiotropium versus omalizumab for patients with severe uncontrolled allergic asthma in US.

Model structure

B2. PRIORITY QUESTION: As per the NICE asthma guideline [NG80], uncontrolled asthma is defined as: 3 or more days a week with symptoms or 3 or more days a week with required use of a SABA for symptomatic relief or 1 or more nights a week with awakening due to asthma. Given the exacerbation lasts for a cycle (4 weeks) in the model, please justify the assumption that the cohort would remain in the controlled asthma state following exacerbation (controlled) and not be allowed to transition into uncontrolled asthma state.

From the call with the EAG we understand this question relates to the non-biologic eligible (3+ exacs OR mOCS) subgroup.

The transition probabilities (which for this subgroup can be seen in Table 104 of the company submission document) are derived directly from trial count data from the NAVIGATOR and SOURCE studies. The counts for this subgroup can be seen in Table 20 of this response document.

For this subgroup, the tezepelumab arm of the SOURCE data (patients on mOCS) found there to be no patients who following exacerbation were uncontrolled having been controlled prior to exacerbation, hence the transition probability in the model is zero percent for the pre-response assessment period (and also the post-response assessment period). For patients not on mOCS, the tezepelumab arm of the NAVIGATOR data showed there were patients who were uncontrolled following exacerbation having previously been controlled, hence the corresponding transition probability is non-zero, both pre- and post-response assessment.

As can be seen in Table 17 to Table 20, counts at the subgroup level are very small, however they are cohesive in that when aggregated they represent the data for the target population for the appraisal: Adults and adolescents 12 years and older with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year OR are on mOCS.

B3. While the model makes a distinction between controlled and uncontrolled exacerbations, such a distinction has not been observed in the NAVIGATOR and SOURCE trials. Please clarify this discrepancy.

The purpose of the economic model is to capture differences in HRQoL and costs across intervention and comparators. Within the NAVIGATOR and SOURCE clinical data the exacerbation distribution differed between patients who were controlled and uncontrolled (defined as ACQ-6 score: <1.5 or >1.5 respectively) prior to exacerbation, as can be seen in Tables 105–108 of the company submission. Generally, the proportion of exacerbations resulting in hospitalisation or A&E visit for patients who were uncontrolled was greater than for those who were controlled. These types of exacerbations are associated with a greater reduction in HRQoL and higher cost than exacerbations resolved by OCS burst. Control status differed between tezepelumab and placebo, hence it was useful to structure the model in this way to capture these differences.

Asthma mortality estimates

B4. The CS mentioned that the asthma mortality life table values were derived using proportion of deaths due to asthma multiplied by the UK general population life table. However, the proportion of deaths used to derive the asthma mortality life table has not been provided. Please provide the proportion of deaths used and explain the calculation for asthma mortality life tables if necessary.

The proportion of deaths attributed to asthma is based on ONS mortality statistics.[5] The query for the statistics was taken using the following:

- Geography selection: all countries available (England and Wales)
- Data selection: 2020 (most recent available)
- Age selection: all available age bands
- Rate selection: deaths
- Sex selection: males and females
- Underlying cause selection: ICS-10 classification codes J45 to J46 for asthma and status asthmaticus

A summary of the number of deaths per age and sex distribution is provided in Table 7. The percentage of asthma deaths is simply calculated as the ratio of asthma deaths to total deaths.

Table 7. Proportion of UK deaths attributed to asthma using ONS statistics[5]

Age band	Asthma deaths		Total deaths		Percentage of asthma deaths	
	Males	Females	Males	Females	Males	Females
<1	0	0	1,333	1,048	0.00%	0.00%
1 to 4	1	0	185	140	0.54%	0.00%
5 to 9	2	0	142	76	1.41%	0.00%
10 to 14	4	0	157	126	2.55%	0.00%
15 to 19	3	3	438	235	0.68%	1.28%
20 to 24	3	3	851	335	0.35%	0.90%
25 to 29	3	5	1,166	534	0.26%	0.94%
30 to 34	4	8	1,645	919	0.24%	0.87%
35 to 39	7	8	2,429	1,488	0.29%	0.54%
40 to 44	6	15	3,385	2,091	0.18%	0.72%
45 to 49	12	20	5,529	3,550	0.22%	0.56%
50 to 54	15	29	8,811	5,612	0.17%	0.52%
55 to 59	21	27	12,758	8,122	0.16%	0.33%
60 to 64	13	26	16,876	11,190	0.08%	0.23%
65 to 69	25	37	22,982	15,229	0.11%	0.24%
70 to 74	29	57	35,562	25,316	0.08%	0.23%
75 to 79	49	88	43,008	33,356	0.11%	0.26%
80 to 84	69	153	52,410	46,906	0.13%	0.33%
85 to 89	80	199	52,083	58,421	0.15%	0.34%
≥90	78	234	46,319	85,159	0.17%	0.27%

In order to calculate the age and sex distributed asthma mortality tables, general population mortality probabilities are multiplied by the proportion attributed to asthma. An example for a 40-year-old male is presented in Table 8 below.

Table 8: An example of a 40-year old male mortality risk

General population mortality risk[6]	Proportion of deaths attributed to asthma	Asthma mortality risk
0.003577	0.17%	0.000006

B5. PRIORITY QUESTION: The CS and the model mentioned that the asthma exacerbation related mortality risk estimates were based on NICE TA565. Though the approach used to derive the asthma mortality risk estimates was in line with TA565, the estimates were not adjusted based on the British Thoracic Society (BTS) adult asthma audit report (2016) as was done in TA565 and TA751. Please explain why adjustment based on the BTS asthma report (2016) has not been done?

We can comment from the perspective of TA565, for which the marketing authorisation of the appraised drug (benralizumab) is also held by AstraZeneca. During the TA565 appraisal process, the ERG requested that the BTS audit data be used as a scenario: Within TA565, the purpose of the adjustment using the BTS adult asthma audit report (2016) was to capture the fact that based on data available at the time, asthma mortality was declining, as can be seen in the standardised asthma mortality rate data for England presented in Table 9 (it’s likely that 2013-15 was the most recent data period at the time benralizumab was being appraised). However, since that time, the subsequently published data shows there has been a marked increase in asthma-related mortality (of up to 10%, in relative terms). As such, it was not appropriate to make the corresponding adjustment for the current submission. Furthermore, as demonstrated at section B.3.8.4.1. of the company submission, even without the adjustment, it is likely that the model underestimates asthma-related mortality when compared with real world mortality in severe asthma patients.

Table 9: Mortality rate for asthma in England (3 year range) [7]

Time period	Count	Directly standardised rate - per 100,000		
		Value	95% Lower CI	95% Upper CI
2006 - 08	2,978	2.25	2.17	2.33
2007 - 09	2,927	2.19	2.11	2.27
2008 - 10	2,914	2.15	2.07	2.23
2009 - 11	2,896	2.10	2.02	2.18
2010 - 12	2,991	2.12	2.05	2.20
2011 - 13	3,073	2.14	2.07	2.22
2012 - 14	3,136	2.14	2.06	2.21
2013 - 15	3,303	2.22	2.14	2.29
2014 - 16	3,435	2.26	2.18	2.34
2015 - 17	3,626	2.35	2.27	2.42
2016 - 18	3,738	2.38	2.31	2.46
2017 - 19	3,771	2.36	2.29	2.44

Abbreviations: CI, confidence interval.

B6. Please include a scenario in the model assuming zero asthma mortality risk reflecting the observation in the trial (no death occurred during the on-treatment period in the tezepelumab or placebo groups [NAVIGATOR CSR, Section 12.2.1.1]).

A new scenario is provided below which assumes zero asthma-related mortality risk. However, the below bullet points provide further information on death occurring during the RCTs:

- NAVIGATOR: No deaths occurred during the on-treatment period in the Tezepelumab or placebo group. A total of two deaths were reported on-study in the placebo treatment group, which were assessed as not causally related to investigational product (IP).

Table 10: Adverse Events with Outcome of Death for the Placebo treatment group - Key Subject Information, On-Study Period (Safety Analysis Set)

Sex	Age[a] (years)	Event term as reported by the investigator	Adverse event (MedDRA Preferred Term)	Time from first dose to AE (days)	Study Period	Time from last dose to death (days)	Time from first dose to death (days)	Received treatment for AE	Reasonable possibility AE causally related to IP[b]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: NAVIGATOR CSR section 12.2.1.1

[a] Age at study entry, [b] As assessed by the investigator. Includes adverse events with an onset date ≥ the first day of study treatment and ≤ (study completion or withdrawal date). Time from variables are calculated as End date - Start date + 1. (Note that programmed safety narratives in Section 14.4 calculate time from variables as End date – start date).

The on-treatment study period includes events with an onset date between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).

The Follow-up period: starts the day after the on-treatment period.

Abbreviations: AE, adverse event; CSR, Clinical study report; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Teze, Tezepelumab

- SOURCE: One death reported (PT: cardiac arrest), which occurred in the tezepelumab group during the on-treatment period.

Table 11: Adverse Events with Outcome of Death for the Tezepelumab 210 mg Q4W group - Key Subject Information, On-Study Period (Safety Analysis Set).

Sex	Agea (years)	Event term as reported by the investigator	Adverse event (MedDRA Preferred Term)	Time from first dose to AE (days)	Study Period	Time from last dose to death (days)	Time from first dose to death (days)	Received treatment for AE	Reasonable possibility AE causally related to IPb
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: SOURCE CSR section 12.3.1

a Age at study entry. b As assessed by the investigator

Includes adverse events with an onset date ≥ the first day of study treatment and ≤ (study completion or withdrawal date). Time from variables are calculated as End date - Start date + 1.

The on-treatment study period includes events with an onset date between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).

The Follow-up period: starts the day after the on-treatment period.

Abbreviations: AE, adverse event; CSR, Clinical study report; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Teze, tezepelumab

- Pathway CSR section 12.3.1.1: One subject in the 70 mg Q4W tezepelumab group (not the licensed dose) in the as-treated population died during the study due to cerebrovascular accident.

Scenario assuming zero asthma mortality risk:

Within the company submission model, asthma mortality is linked to exacerbations. However, to avoid double counting of asthma-related mortality, the all-cause mortality is adjusted to exclude asthma-related mortality. For this scenario, the mortality linked to exacerbations was set to zero (Exacerbations!J195:X206) and the adjustment to all-cause mortality was also set to zero ('Life Tables'!J129:K229). In addition, each of the model engines (*productname* Trace!DY14:EA793) were modified to reflect all-cause mortality. As such, this scenario only considers general all-cause mortality.

In the fully incremental analyses for the anti-IL-5 eligible patients (Table 12), 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 in Table 12.

Pair-wise analyses for tezepelumab versus dupilumab and omalizumab are presented in Table 13 and Table 14, respectively.

Table 13 shows that tezepelumab was dominant versus dupilumab, with QALY gains of [redacted] and cost savings of [redacted] in the dupilumab NICE-recommended population. Similarly, Table 14 shows that 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.

Pair-wise analysis for tezepelumab versus SoC for the non-bio eligible population is presented in

Table 15. Tezepelumab was associated with an incremental cost of [redacted] and a QALY gain of [redacted], resulting in an ICER of £66,241 per QALY gained.

Pair-wise analysis for the reslizumab eligible population is presented in Table 16. Tezepelumab was dominant vs. reslizumab with a QALY gain of [redacted] and cost savings of [redacted]

Table 12: Scenario: Excluding asthma mortality (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]	£483,054	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.

Table 13: Scenario: Excluding asthma mortality (dupilumab 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]	-	-	-		
Dupilumab + 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

Table 14: Scenario: Excluding asthma mortality (omalizumab 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]	-	-	-		
Omalizumab + 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

Table 15: Scenario: Excluding asthma mortality (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£66,241	£66,241

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.

Additionally, results are provided for the reslizumab eligible population in Table 16, as an extension of the response to question B11.

Table 16: Scenario: Excluding asthma mortality (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]	-	-	-		
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

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.

Whilst a zero asthma mortality scenario aligns with the findings of the randomised control trials, it does not align with outcomes for severe asthma patients in clinical practice in England and Wales, to whom this tezepelumab technology appraisal relates. In the response to question B5 we have shown that asthma-related mortality is present and rising and furthermore, as demonstrated at section B.3.8.4.1. of the company submission, it is likely that the cost-effectiveness model under-estimates asthma-related mortality when compared with real world mortality in severe asthma patients.

Transition probabilities

B7. PRIORITY QUESTION: The CS Doc B Section B.3.3.2.1 mentioned that transition probabilities were derived from trial count data and the associated count data transition matrix. Please provide the count data transition matrix used to derive the transition probabilities for all subgroups.

Count data transition matrices for subgroups included in the company submission are provided in Table 17 to Table 20. Additionally, count data are provided for the reslizumab eligible subgroup in Table 21, in relation to question B11.

Table 17: Count data (anti-IL-5 eligible)

Tezepelumab: Pre-assessment with OCS				
	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				
	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				
	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				
	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				
	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				
	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. 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: Count data (dupilumab eligible)

Tezepelumab: Pre-assessment with OCS				
	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: Pre-Assessment without OCS				
	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				
	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				
	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				
	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				
	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. 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 19: Count data (omalizumab eligible)

Tezepelumab: Pre-assessment with OCS				
	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				

	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				
	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				
	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				
	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				
	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. 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 20: Count data (non-bio eligible [3+ exacerbations OR mOCS])

Tezepelumab: Pre-assessment with OCS				
	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				
	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				
	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				
	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				
	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				
	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. 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 21: Count data (reslizumab eligible)

Tezepelumab: Pre-assessment with OCS				
	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: Pre-Assessment without OCS				
	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				
	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				
	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				
	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				
	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; NA, not applicable; OCS, oral corticosteroid. 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.

B8. The CS Doc B Section B.3.3.2.2 mentioned that the transition probabilities between controlled and uncontrolled asthma were assumed to be equivalent across all biologics in the base case. Please provide further rationale for this assumption.

Within the model, control status is a function of ACQ-6. Whilst ACQ change from baseline was assessed in the NMA, different versions of the ACQ questionnaire, which are not directly comparable, were used in the trials of the biologics considered by the model (some used ACQ-5, some ACQ-6, some ACQ-7). This is further described in appendix D.2.1 of the company submission. The NMA found that the differences in ACQ change from baseline between biologics were small and significantly less than the minimum clinically important difference for all versions of ACQ, which is 0.5.[8] As such it was decided for the base case to assume equal control status across biologics in the model.

Proportion of exacerbations

B9. PRIORITY QUESTION: Please justify the application of NMA-derived relative annual hospitalisation rates (ITT population) for uncontrolled exacerbations with OCS for all biologics while assuming equal rates for uncontrolled exacerbations without OCS (economic model, sheet Data library, rows 116-121).

As noted in Section B.3.3.2.2 of the company submission, the annual hospitalised exacerbation rates NMA did not distinguish between patients on mOCS or not, or whether they were responders or not. As such the same relative treatment effect was applied in the model irrespective of mOCS and responder status. In the context of the model, the cells indicated in the question (Data library, rows 116-121, specifically column M contains the ‘active’ values) are then used on the Dashboard sheet, rows 67, 70, 73 & 76, which reflect the controlled with OCS, controlled without OCS, uncontrolled with OCS and uncontrolled without OCS subgroups respectively. The relative effect is applied to all annual hospitalised exacerbation rates (not just for uncontrolled exacerbations with OCS as implied by the question).

It should be noted that there was no equivalent NMA available to assess treatment differences across the biologics with regards to the proportion of AAER leading to an OCS burst, or A&E visit. As such, the model assumes the proportion of requiring an OCS burst, or A&E visit are equal for all biologics.

Utilities

B10. PRIORITY QUESTION: CS Doc B Section B.3.4.1 mentioned that tezepelumab treatment was associated with certain utility gain over and above the gain in HRQoL captured by ACQ score and exacerbation. Please explain what drives this utility gain and why it is assumed equal over all treatments?

The utility regression equation identified that, irrespective of asthma control status or exacerbations, treatment with Tezepelumab was independently associated with a utility gain of 0.05. It is incorrect to say that this utility gain is seen over and above HRQoL captured by ACQ score, however, as it is in line with improvements seen in ACQ score. The question can be answered in two parts, elements of HRQoL which are not captured within ACQ and exacerbations, and elements of ACQ that the model structure does not capture fully.

Elements of HRQoL which are not captured within ACQ and Exacerbations

The ACQ-6 does not capture FEV1 and airway hyperresponsiveness, which are both endpoints which would be expected to have an impact on a patients’ quality of life. FEV1 is captured within the ACQ-7, however this was not captured in the trial.

Elements of ACQ that the model structure does not capture fully

The economic model categorises patients into health states defined by a patients ACQ score, “Controlled” defined as ACQ-6 < 1.5 and “Uncontrolled” defined as ACQ-6 ≥ 1.5. The ACQ-6 is a HRQoL tool which generates scores on a scale between 0 and 6, however, its use in the economic model limits these scores into a binary “controlled” or “uncontrolled”. There is, therefore, the possibility of a patient with an ACQ score of 0, and a patient with an ACQ score of 1.49 being assigned the same utility score, as both of them would be categorised as being “controlled”. The same is true of the “uncontrolled” state.

In order to explore this as an explanation for the difference in utility score seen in the regression model, an analysis of ACQ score by treatment arm was conducted for patients who were classified as Controlled, and Uncontrolled. This analysis showed that patients receiving Tezepelumab consistently had lower ACQ scores than those patients receiving placebo, despite being in the same health state as shown in the Figure 2 and Figure 3. The results of this analysis are attached as embedded file below.

Figure 2: Controlled health state, ACQ score Tezepelumab vs Placebo

[redacted]

Definition: Controlled ACQ-6 at each visit includes subjects with well controlled (ACQ-6 score ≤ 0.75) or partially controlled ACQ-6 (0.75 < ACQ-6 score <1.5). Abbreviation: ACQ, Asthma Control Questionnaire.

Figure 3: Uncontrolled health state, ACQ score Tezepelumab vs Placebo

[redacted]

Definition: Uncontrolled ACQ-6 at each visit includes subjects with ACQ-6 score ≥ 1.5. Abbreviation: ACQ, Asthma Control Questionnaire.

[redacted]

[redacted]

As there is no evidence of a clinically meaningful difference between tezepelumab and the other biologics in terms of ACQ and FEV1 and given tezepelumab's positive impact on airway hyperresponsiveness, the conservative assumption was made that all biologics would receive the utility benefit seen with tezepelumab in the regression model.

Comparator

B11. PRIORITY QUESTION: The CS mentioned that reslizumab has been excluded as a comparator in the model as it is not representing established NHS practice in the target population. However, TA479 specifically recommends reslizumab as an option, and TA565 and TA751 had included reslizumab as a comparator for the relevant target population. Please provide further rationale for this exclusion.

Despite being on the market since 2017, the use of reslizumab in the UK is extremely low making up only 0.6% of all prescribed biologic therapies for severe asthma.[9] For this reason it is not the mainstay treatment option for patients and so is not considered standard of care for biologic eligible patients. However, for completeness we have provided an analysis versus reslizumab + SoC here. Methods employed were the same as for other biologic comparisons as described in the company submission and information on reslizumab eligible population-specific inputs follows:

Details for the modelled population can be seen in Table 22.

Baseline characteristics mirrored those as presented in Table 100 of the company submission for the anti-IL-5 eligible population, as reslizumab is an anti-IL-5 biologic.

Table 22: Indicated and modelled patient populations for reslizumab + Soc[10]

Comparator†	Licensed population	Modelled population and definition	Modelled dosage	Comment
Reslizumab + SoC	As add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment	**Reslizumab eligible** Age 18+ AND 3+ Exacs AND 400+ EOS AND non-mOCS	Modelled dosage: 225 mg (assuming mean weight 77.84kg)	Modelled population aligns with NICE recommended population for reslizumab

Abbreviations: EOS, eosinophil; SoC, standard of care.

Transition probabilities are presented in Table 23. They were derived using observed counts for the reslizumab eligible population from the NAVIGATOR trial which can be seen in Table 21. The NICE recommendation for reslizumab does not include patients on mOCS.[11] Exacerbation distributions are presented in

Table 24.

Table 23: Transition probabilities (reslizumab eligible)

Tezepelumab: Pre-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: Pre-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]
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: mOCS, maintenance oral corticosteroid treatment; 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 24: Exacerbation distributions (reslizumab eligible)

		With OCS			Without OCS		
		Mean	**SE**	**Source**	**Mean**	**SE**	**Source**
Controlled	**Tezepelumab**						
	OCS burst	NA	NA	NA	[redacted]	[redacted]	NAVIGATOR
	A&E visit	NA	NA		[redacted]	[redacted]	
	Hospitalisation	NA	NA		[redacted]	[redacted]	
	SoC						
	OCS burst	NA	NA	NA	[redacted]	[redacted]	NAVIGATOR
	A&E visit	NA	NA		[redacted]	[redacted]	
	Hospitalisation	NA	NA		[redacted]	[redacted]	
Uncontrolled	**Tezepelumab**						
	OCS burst	NA	NA	NA	[redacted]	[redacted]	NAVIGATOR
	A&E visit	NA	NA		[redacted]	[redacted]	
	Hospitalisation	NA	NA		[redacted]	[redacted]	
	SoC						
	OCS burst	NA	NA	NA	[redacted]	[redacted]	NAVIGATOR
	A&E visit	NA	NA		[redacted]	[redacted]	
	Hospitalisation	NA	NA		[redacted]	[redacted]	

Abbreviations: A&E, Accident and Emergency; IL, interleukin; NA, not applicable; OCS, oral corticosteroid; SE, standard error; SoC, standard of care.

As reslizumab is not recommended for patients on mOCS,[11] it wasn't necessary to consider mOCS dose reduction magnitudes in the reslizumab eligible subgroup.

The natural discontinuation rate used was that as given for patients without mOCS as presented in Table 113 of the company submission. Probability of discontinuation at response assessment is provided in Table 25. The value for reslizumab was assumed to be equal to that of tezepelumab in the reslizumab eligible population, as there was no NMA data to inform relative rates.

Table 25: Tezepelumab discontinuation probability: 52-week response assessment (4-weekly rate)

Population	Probability of discontinuation					
	With mOCS			Without mOCS		
	Mean rate	SE	Source	Mean rate	SE	Source
Reslizumab eligible	NA	NA	NA	[redacted]	[redacted]	NAVIGATOR

Abbreviations: mOCS, maintenance oral corticosteroid treatment; NA, not applicable; SE, standard error.

NMA inputs are presented in Table 26. The high blood EOS level (≥300 cells/µL) subgroup NMA was used to inform relative annual exacerbation rate for base case and a scenario was run using the ≥3 Exacs in last 12 months subgroup NMA, as these NMAs best aligned with reslizumab's NICE recommendation.[11] No input was needed for relative mOCS reduction given reslizumab's recommendation.

Table 26: NMA Inputs - OR vs tezepelumab + SoC (reslizumab eligible)

Endpoint	Mean	Log (SE)	Source
Relative annual exacerbation rate (base case)	1.43	0.33	High blood EOS level (≥300 cells/µL) subgroup NMA
Relative annual exacerbation rate (scenario)	1.15	0.62	≥3 exacerbations in the prior 12 months subgroup NMA
Relative annual hospitalised exacerbation rate (base case)	3.45	0.70	Reduction in AAER leading to hospitalisations NMA

Abbreviations: AAER, annualised asthma exacerbation rate; EOS, eosinophil; NMA, network meta-analysis; OR, odds ratio; SE, standard error; SoC, standard of care

Drug acquisition costs for reslizumab (list price) are presented in Table 27. Reslizumab is used in conjunction with SoC, for which the cost is presented in Table 132 of the company submission. Dosing frequency for reslizumab is presented in Table 28.

Table 27: Drug acquisition costs

Intervention	Mean	Source
Reslizumab (list price)	£1,124.97	BNF 225 mg (assuming mean weight 77.84 kg)[12]

Abbreviations: BNF, British National Formulary

Table 28: Number of annual doses

Intervention	Number of annual doses		
	Year 1	Year 2 onwards	Source
Reslizumab	13.0	13.0	Reslizumab Summary of Product Characteristics[10]

Unlike other severe asthma biologics which are patient self-administered subcutaneous injections, reslizumab is in the form of an intravenous infusion. As such it is required to be administered by a health professional in a hospital setting (usually a nurse). The administration costs for reslizumab are detailed in Table 29.

Table 29: Administration costs applied in the economic model

Treatment	Administration time (mins)	Unit cost (per hour)	Cost per administration	Source
Reslizumab	55	£55	£50.42	Reslizumab for treating severe eosinophilic asthma TA479[11] Band 6 Hospital Nurse (PSSRU 2021)[13]

Results of the base case pair-wise analysis for the reslizumab eligible population are shown in Table 30. Tezepelumab was dominant vs. reslizumab with a QALY gain of [redacted] and cost savings of [redacted]

Results for the scenario analysis in which the ≥3 Exacs in last 12 months subgroup NMA was used to inform relative exacerbation rates for the reslizumab eligible population are shown in Table 31. Tezepelumab was dominant vs. reslizumab with a QALY gain of [redacted] and cost savings of [redacted]

Table 30: 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]	-	-	-		
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

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.

Results of the scenario using the ≥3 Exacs in last 12 months subgroup NMA to inform the relative annual exacerbation rate are provided in Table 31.

Table 31: Scenario results – ≥3 Exacs in last 12 months subgroup NMA informs relative AAER (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]	-	-	-		
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

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.

Response assessment

B12. The CS Doc B Section B.3.2.2.3 mentioned that as no clinically meaningful definition of response was available from tezepelumab trials the model assumed response to be any reduction in rate of exacerbation or mOCS dose from baseline. Please explain why, despite trials and NMAs including asthma control outcomes through ACQ scores, asthma control was not used to define the response?

The definition of response is designed to align with that as specified by NICE in it’s recommendations for severe asthma biologics. NICE’s recommendations define adequate response as either reduction in severe exacerbation or mOCS, defined as:

- Meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or clinically significant reduction in continuous oral-corticosteroid use while maintaining or improving asthma control (TA479;[11] TA565;[14] TA671[15])
- NICE (TA751[16]) recommends to stop treatment, if the rate of severe asthma exacerbations has not been reduced by at least a 50% after 12 months.

There is one exception where definition of response is not included (TA278[17]), where it is recommended to continue treatment until they (people currently receiving it) and their clinician consider it appropriate to stop.

B13. The CS and the model assumed the timing of response assessment to be same as tezepelumab (52 weeks) for all biologics. However, this is not consistent with the timing of response assessment used in the respective biologics’ clinical trials. For instance, response to omalizumab was assessed at 16 weeks, and response to mepolizumab was assessed at 32 weeks. Please clarify how these discrepancies were addressed.

NICE’s technology appraisal guidance for all severe asthma biologics except omalizumab states that response should be assessed at 52 weeks.[11,14-16] The model has been aligned accordingly.

Whilst NICE’s guidance for omalizumab makes no stipulation regarding a response assessment[17] we believe such an assessment is conducted in clinical practice in

England and Wales. The company submission inherently assumes this to be at 52 weeks, however we include an additional scenario here whereby omalizumab response is assessed at 16 weeks (with tezepelumab assessment at 52 weeks). Results can be seen in Table 32. Tezepelumab was dominant vs. omalizumab with a QALY gain of [redacted] and cost savings of [redacted].

Table 32: Results for the scenario with omalizumab response assessment conducted at 16 weeks (omalizumab 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]	-	-	-		
Omalizumab + 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.

Deterministic sensitivity analyses

B14. When the DSA macro is run in the CS model, tornado diagrams are not being generated. Kindly amend the model as needed.

The DSA in the model was functional, however the minimum and maximum bounds for the x-axis had been manually set and so in certain scenarios the chart may appear in error (this was simply a display issue)

The model has been updated so that the user will need to:

- From the **Model Control** tab change cell **E8** to **DSA**
- Click the **Access DSA** setup button
- The model will jump to the **_Parameters** sheet
- The user can then select the comparator of interest (Dropdown in cell **F1**)
  - The user can also modify the output of interest in cell **G1** by manually modifying the formula
- The user can then click on the **Generate** Tornado Diagram button
- The model will then run the DSA, this may take several minutes
- Once the analysis is run the model will move to the Tornado Diagram tab
  - The user may need to manually modify the minimum and maximum bounds for the x-axis to optimise the visualisation

Systematic literature reviews

B15. The PRISMA flow diagram (Figure 104, Appendix I) for the cost and healthcare resource use SLR indicates that 38 relevant records were identified after full-text screening, including 28 abstracts. One abstract was included. Please provide citations for the other 27 abstracts and clarify why these abstracts were excluded?

There were 38 relevant records identified which reported costs and resource use. A UK-only country restriction was applied to identify studies relevant for the NICE submission which excluded 27 studies. A single conference abstract reporting data for the UK setting was included:

- White L MA, Capobianco C. Clinical outcomes and micro-costing of bronchial thermoplasty in severe asthma in the UK. European Respiratory Journal 2019;54(PA4802).

Table 33: List of non-UK abstract publications included in the original 2017 cost/resource use SLR but not extracted (n=27)

Nr	Author	Citation	Title
1	Braunstahl, G. J.	Clinical and Translational Allergy. Conference: EAACI International Severe Asthma Forum, ISAF.2012;3(no pagination).	Healthcare utilization and indirect cost of treatment associated with severe allergic asthma in a real-world setting
2	Campos, D. F.	Value in Health.2017;20 (5):A202.	Direct and indirect costs of severe uncontrolled asthma in the Brazilian public perspective
3	Casciano, J.	Value in Health.2015;18 (3):A175.	Cost-consequence of eosinophilic asthma among patients treated according to ERS/ATS guidelines
4	Casciano, J.	Annals of Allergy, Asthma and Immunology.2013;1):A40.	Economic and clinical burden of severe asthma with elevated blood eosinophil level
5	Chastek, B.	American Journal of Respiratory and Critical Care Medicine. 2015;191(no pagination).	The few who use the most: Costs of severe and persistent asthma in a us managed care plan
6	Florez Tanus, A.	Value in Health.2017;20 (5):A355.	Asthma-related direct costs and health care utilization by severity in colombia

Nr	Author	Citation	Title
7	Garcia Ruiz, A.	Value in Health.2014;17 (7):A601.	Health related quality of life and health care utilization in primary care patients with moderate/persistent severity asthma
8	Giblin, G.	Irish Journal of Medical Science.2013;182:S453-S454.	Experiences with omalizumab in a specialist asthma clinic
9	Hankin, C. S.	Journal of Allergy and Clinical Immunology.2013;1):AB126.	Estimated prevalence and economic burden of severe, uncontrolled asthma in the United States
10	Husereau, D.	American Journal of Respiratory and Critical Care Medicine. 2017;195(no pagination).	Severe asthma in primary care in Canada: A longitudinal study of the clinical burden and economic impact based on linked electronic medical record data
11	Krysanov, I.	Value in Health.2013;16 (7):A372.	Inhaled corticosteroids (ICS) in treatment of moderate and severe asthma in Russian Federation - Comparative pharmacoeconomic study
12	Lafeuille, M.	Journal of Allergy and Clinical Immunology.2012;1):AB73.	Impact of omalizumab on emergency-department visits, hospitalizations and corticosteroid use in patients with uncontrolled asthma using high-dose inhaled corticosteroids
13	Lizan, L.	European Respiratory Journal. 2013;42(no pagination).	The impact of asthma severity on the total cost of asthma patients in the Valencia Region
14	Martin, C.	Journal of Allergy and Clinical Immunology.2017;139 (2 Supplement 1):AB58.	Disease burden of uncontrolled severe asthma with elevated eosinophil levels
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Nr	Author	Citation	Title
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25	Yu, T. C.	Value in Health.2014;17 (7):A589.	Impact of omalizumab on poor asthma control events and medication utilisation in patients with moderate or severe persistent asthma
26	Zazzali, J.	European Respiratory Journal. 2012;40(no pagination).	Health care claims analysis to quantify the burden of moderate-to-severe asthma
27	Zhang, S.	Chest.2016;150 (4 Supplement 1):827A.	The impact of adherence and exacerbation frequency on health care utilization and associated direct costs in severe asthma

B16. The PRISMA flow diagram (Figure 104, Appendix I) for the cost and healthcare resource use SLR indicates the total number of records excluded at full-text screening is 190, however, the list of excluded studies (Table 39) shows 191. Please confirm the correct number of excluded studies.

As indicated in Figure 140, there were 190 records excluded at full publication review and one record that was unobtainable. Table 39 also includes the citation details of this unobtainable record:

- Ho H et al. Results of acute exacerbation asthma management basing on the usage of paediatric asthma score (PAS) at children's hospital no.1 from October, 2014 to April, 2015. Respirology. 2016.

Erratum

In forming these responses, we have noticed a reporting error within the company submission document. It relates to the values reported for relative annual exacerbation rate from the subgroup NMA for anti-IL-5 biologics, as presented in Table 115 of the company submission. The originally presented and corrected values are shown in Table 34. The correct values were used in the model, so this was merely a reporting error in the company submission document.

Table 34: Correction to relative annual exacerbation rate (anti-IL-5 eligible) as presented in Table 115 of company submission

Intervention		**Relative annual exacerbation rates vs tezepelumab + SoC**		
		Mean	**Log (SE)**	**Source**
Benralizumab + SoC	As presented in company submission	1.59	0.29	High blood EOS level (≥300 cells/µL) subgroup NMA (Section B.2.9.2.1.2)
	Corrected	1.67	0.31	
Mepolizumab + SoC	As presented in company submission	1.22	0.32	
	Corrected	1.12	0.39	

Abbreviations: EOS, eosinophil; IL, interleukin; NMA, network meta-analysis; SE, standard error; SoC, standard of care.

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Professional organisation submission

Tezepelumab for treating severe asthma [ID3910]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Thoracic Society

3. Job title or position	**Chief Executive**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BTS is the professional membership society representating respiratory health care professionals. Funding from membership subscription, journal and conferences.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve asthma control- reduce exacerbations. As a consequence this will reduce health care utilisation and also reduce risk of steroid related side effects. Improve asthma related quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	The technology should be assessed similar to other licenced biologics: Clinical significant treatment response: reduction in exacerbations by at least 50% and/or reduction in reliance on daily steroids by ≥50%.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes- there is an unmet need for patients with severe asthma. Currently licenced biologics are licenced for patients who have raised biomarkers (blood eosinophils and FeNO) or have severe atopic asthma. The unmet need is for 2 groups of patients- 1. Patients who are Biomarker low and therefore do not fulfil criteria for currently licenced biologics. In the phase 3 clinical trials Tezepelumab has been shown to be effective in this group of patients as well as the biomarker high group 2. Some patients (between 10-30%) do not respond to first line biologic therapy. These patients continue to experience exacerbations (data from the UK Severe Asthma Registry shows that this can be up to 4-5 in a 12 month period) which is associated with a significant impact on quality of life, healthcare utilisation and steroid side effects. Tezepelumab will provide an effective second line therapy option for these patients.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are BTS and NICE guidelines on the management of asthma but these do not include specific details about biologics in the management of severe asthma. GINA guidelines are often referred to but these are not specific for the UK. However, biologics can only be prescribed through a severe asthma MDT.
• Is the pathway of care well defined? Does it	Yes is is defined and there is general consensus on the pathway of care that is delivered by severe asthma centres. However, there are differences in 'first choice' biologic therapy in patients who are eligible to more

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	than one biologic but all biologic prescribing and ongoing use complies with prescribing criteria set by NICE and through Blueteq.
• What impact would the technology have on the current pathway of care?	It would increase the proportion of patients who would be eligible for a biologic and would provide the option of second line therapy for patients who are failing a biologic.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes; current care within severe asthma centres. It would be added to the list of (5) licenced biologics
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Severe asthma centres and after ratification of a severe asthma multi-disciplinary team

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1. Severe asthma centres will need to work to increase their capacity. This may also involve an expansion of pharmacy services to allow for increased prescribing and increased in the home care facilities. May also involve an increase in staffing 2. No specific equipment is needed.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes- for the patient group that is ineligible to currently licenced biologics.
• Do you expect the technology to increase length of life more than current care?	It will improve quality of life and reduce incidence of steroid related side effects.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes- in the groups of patients specified above.
12. Are there any groups of people for whom the technology would be more or	None; apart from the 2 groups specified above.

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No. Severe asthma centres are well set up to provide biologic therapy and this technology is an addition to the biologics already in use. Therefore the clinical pathways are anticipated to be the same and there are no additional clincal requirements.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We would anticipate the ‘rules’ to be similar to other biologics in terms of clinical response (reduction in exacerbations, reduction in reliance on daily steroids. This is assessed by the multidisciplinary team and does not include additional testing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes- the overall impact of reduced oral steroid usage on steroid-related comorbidities (osteoporosis, fractures, hypertension, sepsis, diabetes, mood disturbance etc) will not be captured through the standard QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes it is innovative as it is the first biologic that works in a mechanism that is different to the currently licenced biologics. The latter work ‘down stream’ i.e. they inhibit specific pathways within the asthmatic airways. For example the anti-eosinophil biologics inhibit eosinophils and impact on the inflammatory pathway downstream from eosinophils.Tezepelumab is the first biologic to work higher up the inflammatory cascade and therefore has a broader inhibitory action. Therefore it is effective in patients who have high and low blood eosinophil levels.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as detailed above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The phase 3 studies have not highlighted any particular side effects of safety issues.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trial (NAVIGATOR) recruited patients who had ≥2 exacerbations in a 12 month period. In general in the UK, biologics are licenced for patients who have had ≥3 exacerbations. However, the clinical trial showed Tezepeluab to be effective in the group with fewer exacerbations and therefore this can be translated to ongoing effectiveness in patients who have had more exacerbations.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes: - Reduction in exacerbations - Improvement in asthma control - Improvement in quality of life - Improvement in lung function - Reduction in use of daily steroids
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcomes were not used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) for relevant NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	Real world evidence is still accumulating and has not yet been published
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Tezepelumab will help address an unmet need in severe asthma and it is an innovative treatment
- It will be particularly helpful for patients who do not fulfil crtieria for currently licenced biologics due to low biomarkers as it has been shown to be effective regardless of blood eosinophil level and for patients who have failed first line biologic therapy
- It will reduce exacerbations, improve quality of life and reduce comorbidities related to oral steroid use; as of yet not specific safety issues/ side effects have been noted
- Treatment pathways for the use of biologics already exist and Tezepelumab will be an additional treatment option
- Due to increased number of eligible patients an increase in capacity in severe asthma centres will be needed

Thank you for your time.

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NHS organisation submission (CCG and NHS England)

Tezepelumab for treating severe asthma [ID3910]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England and Improvement (Specialised Commissioning)**

3. Job title or position	National Programme of Care Manager – Internal Medicine
4. Are you (please tick all that apply):	X☐ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England Specialised Commissioning Team**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. British Thoracic Society/ SIGN asthma guidelines: these discuss the assessment and initial management of difficult and severe asthma 2. GINA guideline 2021: covers difficult and severe asthma and the use of biologic However there is no published guidance on biologic choice and clinicians prescribe biologics based on recommendations provided in NICE Technology Appraisals (TAs).
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care, once a patient is referred to a severe asthma centre, is well defined. There is little variation in this pathway in England and in general there are minimal differences of opinion between professionals. All patients who are started on a biologic are discussed by the severe asthma multi-disciplinary team for approval and ongoing use. Severe asthma services are commissioned in England according to the national service specification https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf
8. What impact would the technology have on the current pathway of care?	Current pathway: 1. Patients with severe eosinophilic asthma with raised biomarkers are offered one of 3 biologics 2. Patients with severe atopic asthma with raised biomarkers are offered omalizumab 3. About 20% of patients will not gain clinical benefit from the biologic and would continue to have frequent asthma exacerbations (average 3-4 per year) with impact on daily life and overall health due to side effects of steroids. In most cases they are switched to another biologic 4. Even while on a biologic, most patients will continue to have ~1 exacerbation/ year. 1. Tezepelumab would be another option that could be used when switching biologics 2. While most patients with severe asthma (~80%) will have raised biomarkers at some point, there are some patients who remain biomarker low and continue to have exacerbations and steroid courses which negatively impact on quality of life. In addition to benefitting patients who are biomarker high,

	Tezepelumab (NAVIGATOR study) has been shown to be effective in reducing exacerbations in patients who are biomarker low and it would therefore be a treatment option for this group of patients. This would be hugely beneficial as no other biologic has been shown to be clinically effective in biomarker low patients.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Not currently used. If approved for use, it will be used in nationally commissioned severe asthma centres only which are required to have robust MDT processes that ensure appropriate use of biologics.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We would anticipate it being used in a similar way to the other biologics.
• How does healthcare resource use differ between the technology and current care?	The technology would be reserved for patients with severe asthma who have been assessed in a severe asthma centre. We would anticipate that the healthcare resource use would be similar to that of other biologics; patients are initiated on a biologic at the centre and most patients then self-administer at home after the first 3-6 doses.
• In what clinical setting should the technology be used? (For example,	Severe asthma centres i.e. specialist clinics

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It is likely that most services will need an expansion to accommodate the additional patients who will be started on this drug i.e. some increase in nursing capacity, admin capacity. No additional equipment or training would be mandated. It is likely that the increase in numbers of patients on biologics will increase - this will lead to an increased need for multi-disciplinary team members and/or capacity
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The rules are yet to be decided by NICE. Biomarker assessment is usually carried out just before biologic initiation - this testing is usually part of standard clinical care. Similarly, adherence to prescribed therapy would need to be assessed and this is also part of standard clinical care.
11. What is the outcome of any evaluations or audits of the use of the technology?	The technology is not yet used in clinical practice in most countries. Clinical trials- 1. The NAVIGATOR study showed that patients with severe, uncontrolled asthma who received tezepelumab had fewer exacerbations and better lung function, asthma control and health-related quality of life than those who received placebo (N Engl J Med 2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2034975 2. The PATHWAY study showed that tezepelumab improved patient-reported outcomes in patients with severe, uncontrolled asthma. https://www.nejm.org/doi/10.1056/NEJMoa1704064?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov
Equality	

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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Tezepelumab for treating severe asthma [ID3910]

A Single Technology Appraisal

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
Date completed	27/07/2022
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135524.
Declared competing interests of the authors	None

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Author Contributions:	
Madhusubramanian Muthukumar	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out EAG base case analyses and further scenario analyses, and drafted economic sections of the report
Helen Coelho	Critical appraisal of the company submission, writing and editorial input.
Edward CF Wilson	Critical appraisal of the company submission, drafted economic sections of report, writing and editorial input.
Naomi Shaw	Critical appraisal of the literature search strategies, conducted additional literature searching, and editorial review
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input. Guarantor of the report

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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. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking, the key clinical issue relates to mismatches in subgroups in the network meta-analyses.

In terms of decision modelling issues, the EAG notes the use of an ACQ score of <1.5 to define controlled asthma. This classifies patients with 'partial control' as fully controlled and will thus overestimate the effectiveness of all drugs. The company also excluded reslizumab from its analysis on the basis of infrequent use. Exclusion of a relevant comparator can give rise to misleading cost-effectiveness results.

The EAG further notes that the company employed two sets of transition probabilities, reflecting pre- and post-assessment at Week 52. Whilst non-temporally stationary Markov models are commonplace, modelling transition probabilities as a smooth(er) function of time rather than simple pre-post Week 52 may have been more plausible. The company also applied relative annual hospitalisation and exacerbation rates in a manner which is likely to overestimate the risk of hospitalisation in biologic drugs other than tezepelumab. The model appears to overestimate the risk of asthma mortality and applies a utility gain of approximately [redacted] purely for taking a biological therapy, over and above any treatment effect or incidence of side effects /

adverse events. This was of borderline statistical significance in the company's utility regression model, and does not appear to have any logical grounding, suggesting it is likely a chance finding.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1	Exclusion of reslizumab as a comparator	Section 2.4, Section 4.2.4 and Section 6.3
Key Issue 2	Definition of treatment response	Section 2.4, Section 4.2.6 and Section 6.2.7.1
Key Issue 3	Mismatched subgroups and their provenance in network meta-analyses	Section 3.4, Section 6.2.4 and Section 6.2.5
Key Issue 4	Use of ACQ cut-off score to define controlled asthma	Section 4.2.6.1 and Section 6.2.7.3
Key Issue 4	Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'	Section 4.2.6.3, Section 6.2.1 and Section 6.2.7.2
Key Issue 6	Change in transition probabilities at Week 52	Section 4.2.6.2 and Section 6.2.7.1
Key Issue 7	Hospitalisation rate for biologics other than tezepelumab may be overestimated	Section 4.2.6.3 and Section 6.2.4
Key Issue 8	Asthma mortality may have been overestimated	Section 4.2.8, Section 6.2.2 and Section 6.2.6
Key Issue 9	Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events	Section 4.2.7 and Section 6.2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Comparator	Exclusion of reslizumab	Inclusion of reslizumab	Section 2.4, Section 4.2.4 and Section 6.3
Health state utilities for controlled vs uncontrolled exacerbations	Lower utility assigned to an 'uncontrolled' vs 'controlled' exacerbation.	Equal utility for exacerbation, irrespective of whether 'controlled' or 'uncontrolled'	Section 4.2.6.3, Section 6.2.1 and Section 6.2.7.2

	Company's preferred assumption	**EAG preferred assumption**	**Report Sections**
Asthma mortality risk	Probabilities drawn from various sources based on data from 1981 to 2014	Probabilities calibrated to approximate ONS 2020 data and HSE 2018 asthma report	Section 4.2.8, Section 6.2.2 and Section 6.2.6
Utility gains from biologic therapy	[redacted] increase in utility from being treated with a biologic.	0.00 increase from treatment with a biologic.	Section 4.2.7 and Section 6.2.3
Consequences of exacerbations	Higher risk of hospitalisation for biologics other than tezepelumab	Equal risk of hospitalisation across all biologic therapies	Section 3.3.3, Section 4.2.6.3 and Section 6.2.4
Relative risk of exacerbation for dupilumab	Relative risk of exacerbation for dupilumab derived from Low EoS <300 subgroup	Relative risk of exacerbation for dupilumab derived from High EoS ≥150 subgroup	Section 3.3.3, Section 5.2.3.4 and Section 6.2.5

Abbreviations: ONS, Office of National Statistics; HSE, Health Survey for England

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the time a patient spends in a controlled vs uncontrolled health state
- Reducing the risk of an exacerbation and its consequences on length and quality of life.

Overall, the technology is modelled to affect costs by:

- Incurring the acquisition cost of the various drugs
- Reduced cost of A&E visits and hospitalisations

The modelling assumptions that have the greatest effect on the ICER are:

- Updated estimate for asthma exacerbation related mortality for people <75 years of age
- No additional utility gain assumption for being on biological treatment
- Same exacerbation split as tezepelumab assumed for other biologics and

- Relative risk of exacerbations based on High EOS ≥150 subgroup NMA for dupilumab.

1.3. The decision problem: summary of the EAG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issues for consideration by the committee.

Key Issue 1: Exclusion of reslizumab as a comparator

Report sections	Section 2.4, Section 4.2.4 and Section 6.3
Description of issue and why the EAG has identified it as important	The company excluded reslizumab from their decision model on the grounds that it is very rarely used in clinical practice. Exclusion of a relevant comparator can lead to incorrect conclusions regarding cost-effectiveness.
What alternative approach has the EAG suggested?	Inclusion of reslizumab.
What is the expected effect on the cost-effectiveness estimates?	Not including reslizumab adds further to the existing uncertainty in the decision modelling
What additional evidence or analyses might help to resolve this key issue?	Running the deterministic as well as the probabilistic analysis including reslizumab would help to address this issue. Please note that following the EAG clarification, the company included reslizumab in the model which informs the EAG analysis for the Resli-eligible subgroup.

Abbreviations: EAG, Evidence Assessment Group

Key Issue 2: Definition of treatment response

Report sections	Section 2.4, Section 4.2.6 and Section 6.2.7.1
Description of issue and why the EAG has identified it as important	The response definition assumed in the company submission (i.e., any reduction in exacerbations or mOCS dose from baseline) for tezepelumab is indeterminate and less likely to be clinically meaningful. This was also confirmed by clinical opinion to EAG.
What alternative approach has the EAG suggested?	Clinical opinion to EAG suggested that a 20% or 50% reduction in exacerbations would be considered a clinically worthwhile reduction.
What is the expected effect on the cost-effectiveness estimates?	An alternative and more definitive definition of response would likely change the post-response assessment transition probabilities, which would in turn impact the cost-effectiveness. However, the magnitude and direction of such impact is unknown unless implemented.

Report sections	Section 2.4, Section 4.2.6 and Section 6.2.7.1
What additional evidence or analyses might help to resolve this key issue?	A new set of post-response assessment transition probabilities based on a more definitive response definition would likely reduce the associated uncertainty.

Abbreviations: EAG, Evidence Assessment Group

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the CS. There were no key issues arising from the evidence presented on the three pivotal tezepelumab trials (PATHWAY, NAVIGATOR and SOURCE).[1-3] The EAG identified the following key issue for consideration by the committee.

Key Issue 3: Mismatched subgroups and their provenance in network meta-analyses

Report sections	Section 3.4, Section 6.2.4 and Section 6.2.5
Description of issue and why the EAG has identified it as important	The company's strategy for comparing tezepelumab against other active agents relies on network meta-analysis (NMA), drawing on subgroups generally defined by biomarkers. However, subgroup data are not consistently available for all relevant trials, and no subgroup data are available for the NMA of AAER leading to hospitalisations. This means that model inputs draw on NMAs from a blend of populations, and the provenance of subgroups from included trials is unclear.
What alternative approach has the EAG suggested?	The EAG has used alternative assumptions for the split of hospitalised exacerbations, as the blending of NMA populations generated results that lacked credibility.
What is the expected effect on the cost-effectiveness estimates?	As instantiated, this change has increased ICERs; however, the true effect of using consistent subgroup NMA estimates for every model outcome is unknown.
What additional evidence or analyses might help to resolve this key issue?	Additional data, or more robust assumptions, regarding the population-specific split of exacerbations.

Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; NMA, network meta-analysis

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The ERG reviewed the economic model and cost-effectiveness evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 4: Use of ACQ cut-off score to define controlled asthma

Report sections	Section 4.2.6.1 and Section 6.2.7.3
Description of issue and why the EAG has identified it as important	The company defined 'controlled asthma' as ACQ<1.5. A cut-off of <1.0 would be more appropriate. Patients with an ACQ of 0.75 – 1.5 are defined as 'partially controlled' in the clinical trials. A cut-off of 1.5 will therefore misclassify these patients as controlled and overestimate the effectiveness of treatments.
What alternative approach has the EAG suggested?	The authors of the ACQ suggest a cut-off of 1.0 to be the cross-over point between 'well-controlled' and 'not well-controlled' [Juniper et al. 2006].[4] The EAG's opinion is that this would be a better value to use, reflecting a balance between false negatives and false positives.
What is the expected effect on the cost-effectiveness estimates?	The change is likely to deteriorate (increase) the ICERs of any therapies vs SoC. The impact on comparisons between biologic therapies is unclear.
What additional evidence or analyses might help to resolve this key issue?	Recalculation of the transition probabilities from existing data sources with ACQ <1.0.

Abbreviations: EAG, Evidence Assessment Group

Key Issue 5: Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'

Report sections	Section 4.2.6.3, Section 6.2.1 and Section 6.2.7.2
Description of issue and why the EAG has identified it as important	The model structure differentiates between a patient experiencing controlled vs uncontrolled exacerbations, which conflicts with the clinical opinion to EAG that there is no difference between controlled and uncontrolled exacerbations. This is also somewhat contradictory from a disease perspective as a patient experiencing an exacerbation by definition has uncontrolled asthma. Further, the company model does not allow transitions from the controlled asthma state to uncontrolled exacerbations (or uncontrolled asthma to controlled exacerbation).
What alternative approach has the EAG suggested?	Ideally, the model structure would have a single exacerbation health state. However, given certain transitions were not allowed in the model framework and due to time constraints, a full implementation of a single exacerbation health state was not possible. Therefore, EAG has chosen a simple approach where the utilities for controlled & uncontrolled were

Report sections	Section 4.2.6.3, Section 6.2.1 and Section 6.2.7.2
	set to be the same (note that the costs were already identical for the two exacerbation health states).
What is the expected effect on the cost-effectiveness estimates?	The total QALYs are expected to reduce for all the treatments as there will be an increase in the number of patients transitioning to the uncontrolled asthma and exacerbation health states. The incremental impact, however, depends on the relative reduction in QALYs between the treatments considered.
What additional evidence or analyses might help to resolve this key issue?	Revising the model structure with a single exacerbation health state and re-estimating the transition probabilities accordingly would help to reduce the associated structural uncertainty. Alternatively, allowing the transition from controlled asthma to uncontrolled exacerbations and setting the transition probabilities from controlled and uncontrolled exacerbations to the asthma control states to be equal might have a similar impact.

Abbreviations: EAG, Evidence Assessment Group

Key Issue 6: Change in transition probabilities at Week 52

Report sections	Section 4.2.6.2 and Section 6.2.7.1
Description of issue and why the EAG has identified it as important	The company's model uses one set of transition probabilities prior to Week 52, and a second set post Week 52. Whilst it is common for a model to include transition probabilities that change with time, the 52-week time point is abrupt. A smoother function would be preferable and is more likely to closer reflect reality.
What alternative approach has the EAG suggested?	The EAG was not able to conduct a full re-estimation of transition probabilities. However, a scenario analysis using the constant transition probabilities is explored.
What is the expected effect on the cost-effectiveness estimates?	The post-52-week transition probabilities are more favourable to tezepelumab. However, they coincide with a one-off increase in discontinuations. The effect is therefore unknown.
What additional evidence or analyses might help to resolve this key issue?	Re-estimation of the transition probabilities derived a function of time might reduce the associated uncertainty.

Abbreviations: EAG, Evidence Assessment Group

Key Issue 7: Relative risk of hospitalisation with comparator biological therapies

Report sections	Section 4.2.6.3 and Section 6.2.4
Description of issue and why the EAG has identified it as important	The method of calculation may lead to an overestimate of hospitalisations in biologics other than tezepelumab. The company model calculates the probability of exacerbation for comparator biologic therapies from the NMA. However, it then appears to further multiply the probability of hospitalisation, given an exacerbation, by the relative risk of hospitalisation, rather than the conditional relative risk.
What alternative approach has the EAG suggested?	The EAG suggests a scenario where the risk of hospitalisation given an exacerbation is equal across all biological therapies.
What is the expected effect on the cost-effectiveness estimates?	As there is no difference in hospitalisation risk across biological therapies, the QALY gain in terms of reduction in hospitalisation decreases leading to an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Reanalysis of existing NMA data to estimate the relative risk of hospitalisation, conditioned on a patient experiencing an exacerbation.

Abbreviations: EAG, Evidence Assessment Group; NMA, network meta-analysis

Key Issue 8: Asthma mortality may have been overestimated

Report sections	Section 4.2.8, Section 6.2.2 and Section 6.2.6
Description of issue and why the EAG has identified it as important	The company's model has overestimated asthma mortality for the relatively younger age group (<75 years). Overestimating mortality over-estimates the QALYs gained and thus cost-effectiveness of a treatment that prevents mortality.
What alternative approach has the EAG suggested?	Alternative probabilities of death from patients admitted to hospital.
What is the expected effect on the cost-effectiveness estimates?	With reduced per cycle probabilities of asthma-related deaths in the younger population (<75 years), the QALY gain decreases leading to an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG has calibrated the model to the latest available (2020) ONS asthma mortality data.

Abbreviations: EAG, Evidence Assessment Group; ONS, Office for National Statistics; QALYs; quality adjusted life years

Key Issue 9: Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events.

Report sections	Section 4.2.7 and Section 6.2.3
Description of issue and why the EAG has identified it as important	The company's model includes a utility increment of [redacted] for patients treated with a biologic therapy which is not attached to any health state. The EAG is unconvinced as to the biological plausibility of this increase, given the model already considers the utility gain through changes in asthma control status and reduction in exacerbations and this is of borderline statistical significance.
What alternative approach has the EAG suggested?	Removal of the [redacted] utility increment associated with biological therapy
What is the expected effect on the cost-effectiveness estimates?	Removal of this additional utility gain would have a significant impact on the cost effectiveness of tezepelumab vs standard of care.
What additional evidence or analyses might help to resolve this key issue?	Recalculation of the utility regression equation (and, in particular, the variance/covariance matrix) excluding the coefficient on biologic therapy.

Abbreviations: EAG, Evidence Assessment Group

1.6. Other key issues: summary of the EAG's views

No other key issues were identified.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The ERG's preferred base case results (cumulative) are presented in Table 3.

As part of the preferred base case (cumulative), the EAG considered the following assumptions:

- No difference in utilities for controlled and uncontrolled exacerbations (applicable to all subgroups).
- Asthma mortality risk re-estimated for people <75 years of age (applicable to all subgroups).
- No additional utility gain for being on biological treatment (applicable to all subgroups).
- Exacerbation split (OCS burst/ED visit/Hospitalisation) assumed to be the same as tezepelumab for other biologics (applicable to anti-IL5, reslizumab, dupilumab and omalizumab eligible subgroups).

- Relative exacerbation rate for dupilumab derived from high EOS ≥150 subgroup NMA (applicable to only dupilumab eligible subgroup).

Please refer to Section 6.3, Table 52 to Table 56 for the incremental results and change in each versus the EAG base case. Note the CS presents pairwise rather than fully incremental differences in cost and QALYs. The EAG has corrected increments for benralizumab accounting for this.

Table 3: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Anti-IL5 eligible						
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Reslizumab eligible						
EAG corrected company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
EAG base case - Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]			
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Dupilumab eligible						
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]			
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Omalizumab eligible						
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
EAG base case - Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]			
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Non-bio eligible						
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-

Preferred assumption	**Section in EAG report**	**Total costs**	**Total QALYs**	**Incremental cost**	**Incremental QALYs**	**ICER £/QALY**
EAG base case - Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-
EAG base case - Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	*6.3*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

This report provides a brief review of the evidence submitted by the company (AstraZeneca) in support of tezepelumab for the treatment of severe asthma. It includes evidence presented within the company's submission and responses to the External Assessment Group's (EAG) clarification questions provided by the company.

2.2. Critique of the company's description of the underlying health problem

An overview of asthma is provided in the CS (Document B, Section B.1.3.1 to B.1.3.5).

As described in the CS, asthma is a heterogeneous disease, characterised by chronic airway inflammation, and defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity together with variable expiratory airflow limitation.[5]

The definition of severe uncontrolled asthma in the CS is based on available guidelines Global Initiative for Asthma (GINA) 2022 guidelines[5] and the ERS/ATS 2014 guidelines,[6] and aligned with previous health technology appraisals: asthma that requires high-dose inhaled corticosteroid (ICS)-long-acting beta agonist (LABA) to prevent it from becoming uncontrolled or that remains uncontrolled despite optimised treatment with high-dose ICS-LABA. Evidence for any one of the following criteria for uncontrolled asthma in combination with receipt of a high-dose therapy (i.e. high-dose ICS plus a LABA as specified in the Global Initiative for Asthma [GINA] guidelines) defines a patient with severe, uncontrolled asthma: (1) poor symptom control – defined as: Asthma Control Questionnaire (ACQ) consistently ≥1.5 or Asthma Control Test (ACT) <20; frequent symptoms, activity limited by asthma, night waking; and, frequent rescue reliever use; (2) frequent severe exacerbations (≥2/year) requiring a short course (≥3 days each) of mOCS; and (3) serious exacerbations requiring hospitalisation (≥1/year).

The CS also describes the different subtypes of severe asthma and how, with the increasing use of biologic treatments, inflammatory phenotypes are used to describe asthma populations grouped together by either biomarker expression or perceived underlying inflammatory biology. Key biomarkers include serum specific immunoglobulin E (IgE), blood (and sputum) eosinophils (EOS), and fractional exhaled NO concentration (FeNO).[5,7,8] These are currently used to define different subtypes of asthma, as they are indicative of distinct inflammatory pathways and central to the management of severe, uncontrolled asthma, as biologic treatments are prescribed on the basis of individual inflammatory pathways in current clinical practice. The EAG's clinical expert noted that there would be overlap between the different subtypes of asthma and the groups are not mutually exclusive.The subtype of severe asthma also has an important influence on the comparisons made and analyses presented in the CS.

The company estimates that, of the 5.4 million patients receiving treatment for asthma in the UK,[9] around 4% have severe asthma,[10] of which 65.5% (or 141,000 people) have severe, uncontrolled asthma.[11]

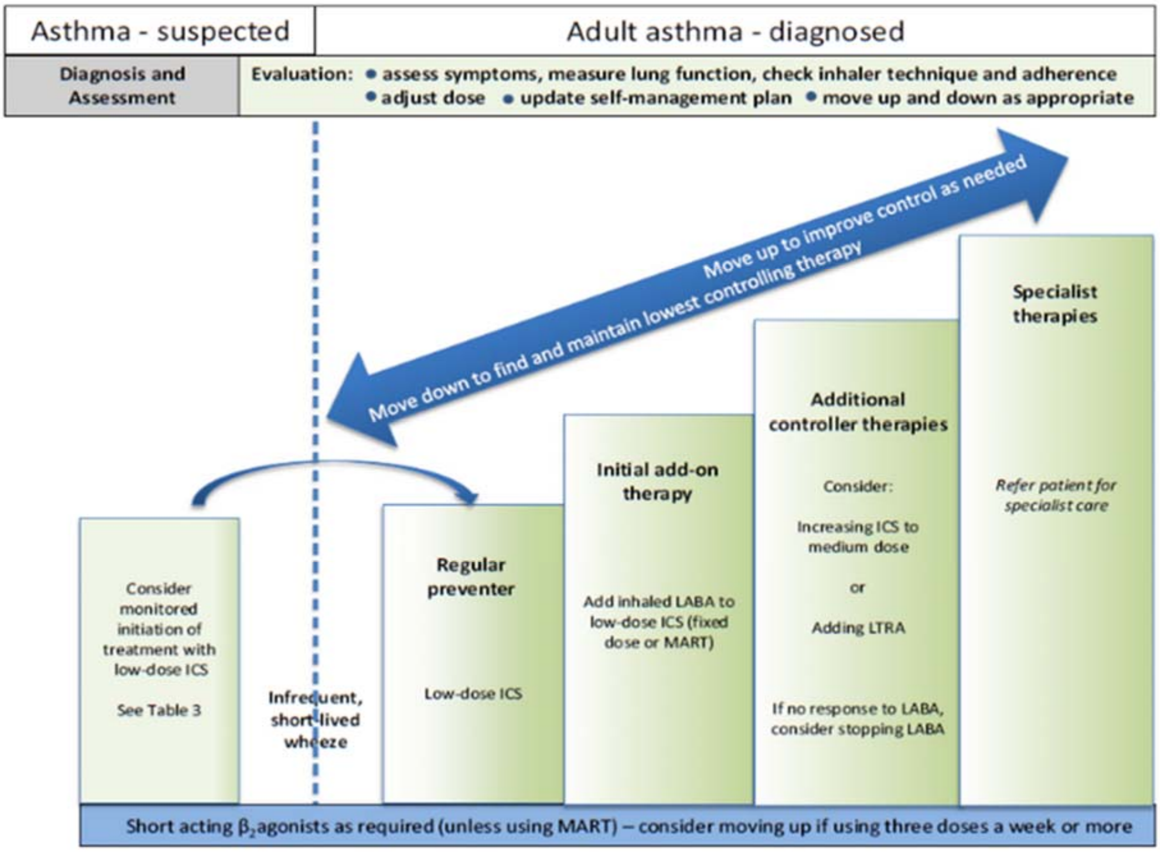
The CS describes the burden of severe, uncontrolled asthma is high due to associated exacerbations and hospitalisations.[12] The unpredictability and distress associated with severe, uncontrolled asthma symptoms has a substantial negative impact on the lives of patients, including a detriment in the ability to perform usual daily activities,[5,13,14] and negatively impacts their mental health.[15] Caring for people with severe asthma has also been shown to impair carer QoL – to a similar degree to that seen in carers of people with COPD and other debilitating diseases such as cancer.[16] Management of severe, uncontrolled asthma is also noted to place a substantial economic burden on healthcare systems.

2.3. Critique of the company's overview of current service provision

The CS describes the clinical pathway of care (Document B, Section B.1.3.6).

The CS notes that in England and Wales, treatment for severe, uncontrolled asthma generally follows the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[17] Guidelines recommend a stepwise approach for treating asthma. Control is maintained by stepping up treatment as necessary using combinations of inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), and long-acting beta-2 agonists (LABAs), and stepping down when control is good. People whose asthma is inadequately controlled by medium-dose ICS plus a LABA with/without an LTRA are typically stepped up to have high-dose ICS or offered a trial of an additional drug. The CS provides an overview of both the BTS/SIGN guidelines (Document B, Section B.1.3.6.1) (see also Figure 1, below), and the GINA guidelines (Document B, Section B.1.3.6.2).

Figure 1. BTS/SIGN – 2019 guideline for the management of asthma in adults/adolescents



Abbreviations: BTS, British Thoracic Society; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; SIGN, Scottish Intercollegiate Guidelines Network

Source: CS, Document B, Section B.1.3.6.1, Figure 2

The CS describes that the NICE guidelines for the treatment of asthma (NG80) do not cover the management of severe asthma or acute asthma attacks,[18] but the NICE pathway for managing asthma includes (under the category of 'difficult and severe asthma') guidance on the use of the currently reimbursed biologics: omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab.[19-24] NICE's recommendations relate to subsets of the patient population with three or more exacerbations in the prior year OR who are on mOCS and reflect the subpopulations defined by biomarkers.

Table 4. NICE technology appraisal guidance for the treatment of severe asthma

Treatment and licensed indication (SmPC)	NICE recommendation
Omalizumab Indicated in adults, adolescents and children (6 to <12 years of age). Omalizumab treatment should only be considered for patients with convincing IgE- mediated asthma Adults and adolescents (12 years of age and older): Omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist Children (6 to <12 years of age): Omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled β2-agonist[6]	Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged ≥6 years who need continuous or frequent treatment with OCS (defined as four or more courses in the previous year)(86).
Reslizumab Indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment[25]	Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug, only if: • Blood EOS is ≥400 cells/µl • There have been ≥3 severe exacerbations in the last 12 months needing SCS[26]
Benralizumab Indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately	Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS and LABA, only if:

Treatment and licensed indication (SmPC)	NICE recommendation
controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists [27]	• Blood EOS is ≥300 cells/µl, and ≥4 exacerbations in the last 12 months needing SCS, or has had continuous OCS of at least the equivalent of prednisolone 5 mg/day over the previous 6 months (that is, the person is eligible for mepolizumab), or • Blood EOS is ≥400 cells/µl with ≥3 exacerbations in the last 12 months needing SCS (that is, the person is eligible for reslizumab)[28]
Mepolizumab Indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older[29]	Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if: • Blood EOS is ≥300 cells/µl, and ≥4 exacerbations in the last 12 months needing SCS, or has had continuous OCS of at least the equivalent of prednisolone 5 mg/day over the previous 6 months, or • Blood EOS is ≥400 cells/µl, and ≥3 exacerbations in the last 12 months needing SCS (that is, the person is eligible for either benralizumab or reslizumab)[30]
Dupilumab Indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment[31]	Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with Type 2 inflammation that is inadequately controlled in people ≥12 years, despite maintenance therapy with high-dose ICS and another maintenance treatment, only if: • Blood EOS is ≥150 cells/µl and FeNO ≥25 ppb, and ≥4 exacerbations in the last 12 months • The person is not eligible for mepolizumab, reslizumab or benralizumab, or has asthma that has not responded adequately to these biological therapies[26]

Abbreviations: EOS, eosinophil; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta agonist; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; ppb, parts per billion; SCS, systemic corticosteroid; SmPC, Summary of Product Characteristics.

In Section B.1.3.7, the company included data from the UK Severe Asthma Registry (UK SAR) (a large national severe asthma registry collecting standardised data on referrals to UK specialist services). A study of UK SAR data assessed biologic treatment patterns for 2,225 patients with severe asthma over the period November 2016 to February 2020.[32] In total, 68.9% of patients were prescribed biologic therapy and the proportion of patients receiving each biologic is presented in Table 5. The most commonly prescribed biologic was mepolizumab, which represented more than half (50.3%) of all prescriptions. Benralizumab (26.1%) and omalizumab (22.6%) were also frequently used, while reslizumab (0.6%) and dupilumab (0.3%)

combined made up <1% of all prescribed biologics. The company does, however, note that the relative proportions likely reflect the duration of availability of the specific therapy at the time of the analysis, the eligible population size, and individual physician preferences.

Table 5: Relative rates of prescribing of biologic therapies currently reimbursed in the UK for the treatment of severe asthma – Data from the UKSAR

Biologic therapy	**n (%)**
Mepolizumab	731 (50.3)
Benralizumab	380 (26.1)
Omalizumab	329 (22.6)
Reslizumab	9 (0.6)
Dupilumab	5 (0.3)

Abbreviations: UKSAR, UK Severe Asthma Registry.

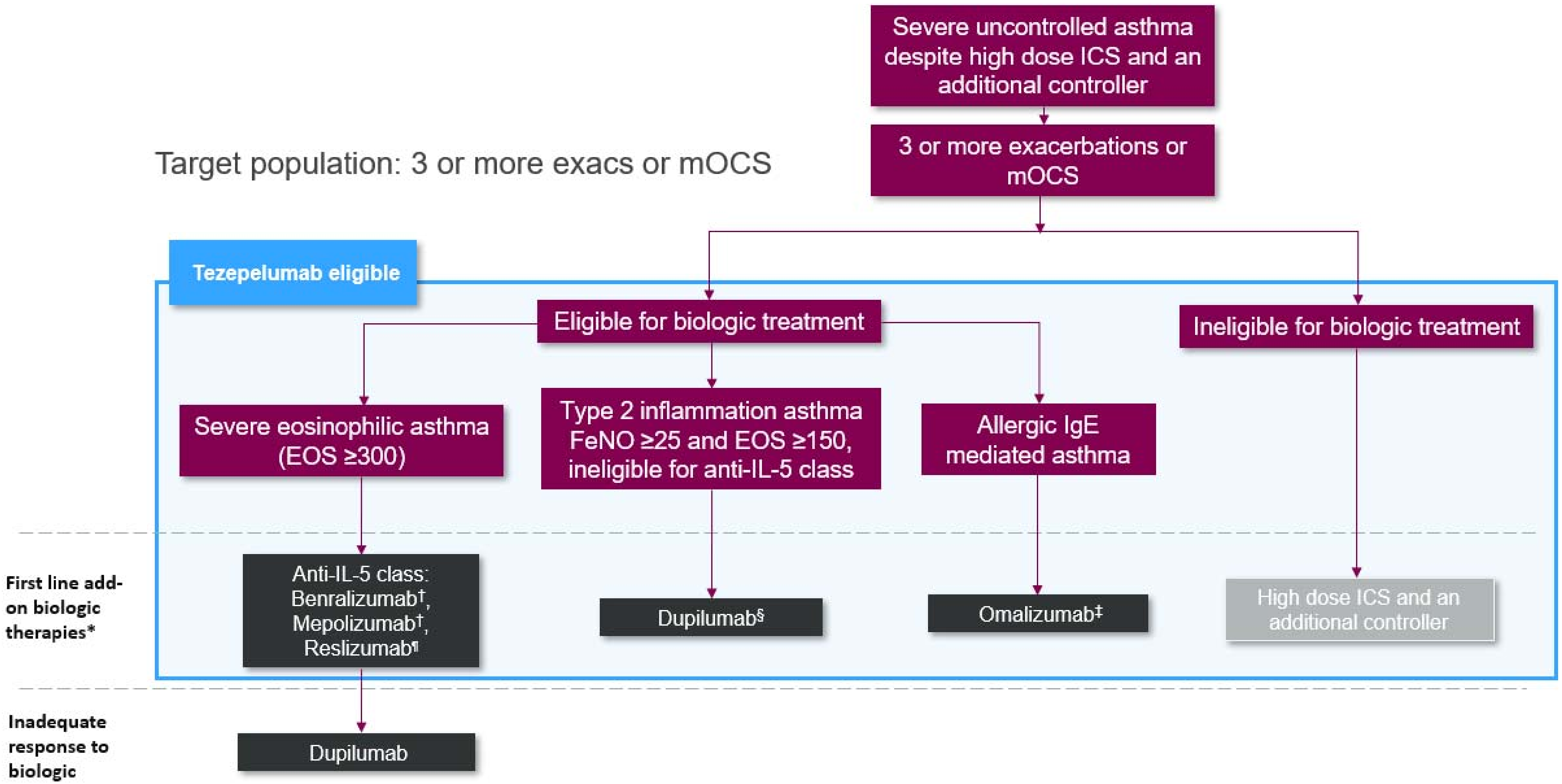
Source: Jackson 2021 [32].

The CS described that in the UK currently, all available biologic therapies for severe asthma are biomarker-specific, meaning that patients must meet biomarker criteria in order to be eligible for treatment with a particular biologic. The company provided an overview of available biologics and their respective eligible patient population (by biomarker profile) indicating proposed tezepelumab positioning (Figure 2).

2.4. Critique of company's definition of decision problem

The company statement regarding the decision problem is presented in Section B.1.1 of the CS. The company position and the ERG response is provided in Table 6.

Figure 2: Current treatment pathway – severe uncontrolled asthma, including tezepelumab



Abbreviations: EOS, eosinophil; exacs, exacerbations; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; mOCS, maintenance oral corticosteroid treatment

† Adults: (400+ EOS AND 3+ exacs) OR 300+ EOS AND (4+ exacs OR mOCS)

¶ Adults: 400+ EOS AND 3+ exacs

§ (Adults: 25+ FeNO AND 150-299 EOS AND 4+ exacs) OR (Age 12-17: 25+ FeNO AND 150+ EOS AND 4+ exacs)

‡ Age 6+: AllEAGic IgE-mediated asthma AND 4+ exacs OR mOCS

* Add-on to high dose ICS + additional controller.

Source: CS, Document B, Section B.1.3.10, Figure 5

Table 6: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People aged 12 years or older with severe asthma that is inadequately controlled by standard therapy	Adults and adolescents 12 years and older with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year OR are on mOCS	The target population reflects where tezepelumab provides the greatest absolute clinical benefit	The model comprises analysis on four sub-populations, defined according to disease subtype and consequent eligibility for different treatment options. The EAG is satisfied that the subgroups are appropriate.
Intervention	Tezepelumab as an add-on to standard therapy	As per scope	NA	Aligned with scope
Comparator(s)	For people for whom biologics are indicated or suitable according to NICE guidance, in addition to standard therapy: • Reslizumab • Benralizumab • Mepolizumab • Omalizumab • Dupilumab (subject to ongoing NICE appraisal) For people for whom currently available biologics are not indicated or suitable: Optimised standard therapy without biologics	As per scope with the exception of reslizumab + SoC	Reslizumab + SoC was excluded as a comparator in economic modelling on the basis of it not representing established NHS practice in the target population.	The company excluded reslizumab as a comparator on the grounds that it does not represent current practice in England: a recent (2021) analysis of the UK Severe Asthma Registry observed that 9/2,225 severe asthma patients received reslizumab (0.4%, or 0.6% of those treated with a biologic).[32] Whilst the NICE methods guide (2013) does state that established NHS practice is a ground for judging the appropriateness of including a comparator, it also states that existing NICE guidance, cost-effectiveness and licensing status of the comparator are also valid criteria. Reslizumab received a positive recommendation from NICE in October 2017.[26] The EAG considers exclusion on the grounds of current practice a weak criterion: a comparator may not represent current practice simply due to lack of promotion/marketing by the manufacturer or novelty of the drug. This does not mean it should not be used or considered in routine practice.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				The EAG considers the fact that reslizumab has received a positive recommendation from NICE a much stronger criterion and therefore it should be included as a comparator.
Outcomes	The outcome measures to be considered include: • Asthma control • Incidence of clinically significant exacerbations, including those that require unscheduled contact with healthcare professionals or hospitalisation • Use of oral corticosteroids • Patient and clinician evaluation of response • Lung function • Mortality • Time to discontinuation • Adverse effects of treatment • Health-related quality of life	As per scope	NA	Aligned with scope. However, the response definition assumed in the company submission (i.e., any reduction in exacerbations or mOCS dose from baseline) for tezepelumab is indeterminate and less likely to be clinically meaningful. This was also confirmed by clinical opinion to EAG. The company model also uses an ACQ cutoff of ≤1.5 to define controlled asthma. This classifies patients with 'partial control' as 'fully controlled', thus exaggerating effectiveness. A score of ≤1.0 would be more appropriate.
Subgroups	If the evidence allows, the following subgroups will be considered: • Baseline EOS levels • Baseline FeNO levels • People who require maintenance OCS treatment • People who require frequent OCS treatment	As per scope. In addition, the following subgroups are considered: • **The anti-IL-5 eligible population:** ◦ Age 18+, 300+ EOS (4+ exacs OR mOCS) OR (400+ EOS AND 3 exacs)	To enable assessment of clinical and cost-effectiveness in the subpopulations in which NICE's recommendations from previous biologic appraisals apply and remaining patients with 3 or more exacs or mOCS who are currently not biologic eligible	The subgroups considered are appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment

		- **The omalizumab eligible population:**
		  - Age 12+, 30+ IgE AND (4+ exacs OR mOCS)
		- **The dupilumab eligible population**:
		  - Age 18+ AND 4+ Exacs AND 150–299 EOS AND 25+ FeNO AND non-mOCS, OR
		  - Age 12–17 AND 4+ Exacs AND 150+ EOS AND 25+ FeNO AND non-mOCS
		- **The 3+ exacs or mOCS non-bio eligible population (people for whom currently available biologics are not indicated or suitable):**
		Age 12+ AND 3+ exacs OR mOCS minus anti-IL-5 eligible minus omalizumab eligible minus dupilumab eligible		

Special considerations including issues related to equity or equality Subgroups	None	Equality for lower eosinophilic disease and gender equality (severe asthma has a higher prevalence in women than men)	Commentary on equality issues is provided in the CS, Document B, Section B.1.4	The company raise equality considerations: (1) equality for patients who do not meet biomarker criteria for currently available biologics and gender equality and (2) describe that severe asthma is known to have a higher prevalence among females compared with males. Throughout their lifetime, females have a higher

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				likelihood of developing asthma and developing a more severe form of asthma than their male counterparts.[33] The company reference the NAVIGATOR trial which included a higher proportion of females with an eosinophilic subtype (01.5% vs 62.9%).

Abbreviations: CS, company submission; EAG, External Assessment Group; EOS, eosinophilic; Exacs, exacerbations; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL-5 interleukin-5; mOCS, maintenance oral corticosteroids; NA, not applicable; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroids

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of tezepelumab for adults and adolescents 12 years and older with severe uncontrolled asthma despite high dose inhaled corticosteroids (ICS) and an additional controller, who experienced three or more exacerbations in the prior year or are on maintenance oral corticosteroids (mOCS).

The EAG reviewed the details provided on:

- Methods implemented to identify, screen, extract data and assess the risk of bias in relevant evidence
- Clinical efficacy of tezepelumab for the stated indication
- Safety profile of tezepelumab for the stated population
- Assessment of comparative clinical effectiveness of tezepelumab against relevant comparators (based on results from a series of NMAs)

A detailed description of an aspect of the CS is only provided where the EAG disagreed with the company's assessment or proposal, or where the EAG identified a particular area of concern that the EAG considered necessary to highlight for the Committee. Otherwise, the EAG signpost to the relevant part of the CS.

As stated in Section 1.4, there were no key issues arising from the data presented from the tezepelumab trials. The EAG identified a key clinical effectiveness issue related to the NMAs, namely the use of mismatched subgroups and their provenance.

3.1. Critique of the methods of review

The Company undertook a systematic literature review (SLR) to identify RCT evidence reporting on the efficacy and safety of tezepelumab for the treatment of patients with severe, uncontrolled asthma. The SLR was originally conducted in October 2020 and then updated in November 2021. A summary of the EAG's critique of the methods implemented in this SLR is presented in Table 7.

The SLR identified three eligible studies of tezepelumab, one Phase II RCT (PATHWAY), and two Phase III RCTs (NAVIGATOR and SOURCE). In addition, 36 RCTs were identified for inclusion in network meta-analyses (NMAs), although one was later excluded because the relevant outcome was only reported for one study arm. Of the remaining 35 studies, three were the key tezepelumab trials, six related to benralizumab, three to dupilumab, three to mepolizumab, 16 to omalizumab and four to reslizumab (see 3.4 for the EAG's critique of the NMAs).

Overall, the EAG found this SLR to be of reasonable quality, although due to the exclusion of non-English language articles, the EAG cannot rule out the possibility that studies may have been missed. However, it was likely that the key studies relevant to the Company's decision problem were identified. The EAG highlight that, consistent with the NICE scope, but contrary to the Company's decision problem and economic modelling, reslizumab was included as a comparator in the SLR and resulting NMAs. The EAG agree that the inclusion of reslizumab as a comparator in the SLR and NMAs is appropriate, and disagree with the exclusion of this comparator in the economic modelling (refer to Section 4.2.4).

Table 7: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	CS Appendix D.1.1	The searches of bibliographic databases and other sources are considered broadly appropriate. The EAG noted in clarification question A1 that controlled vocabulary terms for asthma were not exploded to include narrower terms in the hierarchy (e.g. the EMTREE term for asthma/ was not exploded and the relevant term for eosinophilic asthma/ was not included in the Embase search strategy). The company conducted additional searches using these terms and found no further relevant studies.
Inclusion criteria	CS Appendix D.1.2.1	Although the searches were designed to include all languages, non-English language articles were excluded during study selection. Relevant trials published in other languages may, therefore, have been missed. The EAG note that, as per the NICE scope, reslizumab was

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		included as a comparator in the SLR (alongside omalizumab, mepolizumab, benralizumab, and dupilumab). This differs from the decision problem presented by the company and the economic modelling, which exclude reslizumab (see Section 2.4 for a critique of the Company's definition of the decision problem). The EAG agree with the inclusion of reslizumab in the SLR and resulting NMAs. The inclusion criteria were relaxed to allow the inclusion of studies that reported LABA use in at least 75% of participants, in combination with at least medium dose ICS (even if LABA use or other controllers were not required as a part of the trial inclusion criteria). The EAG agree that this will have enabled a broader capture of evidence for the NMAs, but note that this was not specified in the Company's decision problem. Furthermore, the inclusion of participants using medium-dose ICS differs from the decision problem, which specifies high-dose ICS. It is possible that the inclusion of participants using medium dose ICS runs the risk of including under-treated participants who may be more likely to experience exacerbations but who may also be successfully treated with a higher dose ICS.
Screening	CS Appendix D.1.2.2	Standard accepted methods. The EAG note, that it is unclear (in the CS) how the three pivotal trials were identified (all were designated as 'identified from additional sources'). Following clarification, the Company stated that conference abstracts for all three trials were identified as part of the systematic review process, and that these were supplemented with the CSRs for

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		each study. The EAG agree that chasing CSRs when only conference abstracts were available was a reasonable methodological approach.
Data extraction	Not reported in the CS	Following clarification from the Company, the EAG can confirm that data extraction was performed using standard accepted methods.
Tool for quality assessment of included study or studies	CS Document B.2.5 (for the tezepelumab trials) CS Appendix D.2.1.6 (additional trials included in the NMA)	Different methods were used to assess RoB in the tezepelumab trials (CRD guidance, rather than a standardized RoB tool) and the other trials included in the NMAs (NICE quality appraisal checklist for quantitative intervention studies). Following clarification, and to ensure consistency between the RoB assessments for the tezepelumab trials and those included in the NMAs, the Company provided additional NICE quality appraisal checklist assessments for the tezepelumab trials.
Meta-analysis of pivotal trials	CS Appendix D.5	Post-hoc pooled analyses (data from PATHWAY and NAVIGATOR) were provided, the methods used to conduct these analyses were not described in detail.

Abbreviations: CRD, Centre for Reviews and Dissemination, University of York; CS, Company submission; CSR, clinical study report; EAG, External Assessment Group; ICS, inhaled corticosteroids; LABA, long-acting beta agnoists; NMAs, network meta-analyses

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS describes three pivotal randomised controlled trials (RCTs). The Company supplied the CSR for each of these three trials; PATHWAY,[1] NAVIGATOR,[2] and SOURCE.[3] A primary peer-reviewed publication was available for PATHWAY (Corren 2017),[34] but not for the other two trials. Additional references (i.e. conference abstracts) were also listed in CS Appendix D.1.2.4,

Table 3. PATHWAY,[1] NAVIGATOR,[2] and SOURCE[3] are summarised in Table 8 and a critique of the methods and results of these trials is provided in Sections 3.2.2 and 3.2.3.

PATHWAY (NCT02054130)[1] is a Phase II, multicentre, dose-ranging, double-blind, placebo-controlled RCT, conducted across 12 countries, comparing three different doses of tezepelumab with placebo, all given in addition to standard of care (SoC). A tezepelumab 210 mg SC Q4W + SoC group was included (see Table 8). NAVIGATOR (NCT03347279)[2] and SOURCE[3] are both Phase III, multicentre, double-blind, placebo-controlled RCTs, with NAVIGATOR[2] conducted across 18 countries and SOURCE[3] across seven countries.

The review also identified 35 trials that were included in NMAs, some of which were used to inform the economic model (see Section 3.3).

Table 8: Clinical evidence included in the CS

Study name	Study design	Population	Intervention	Comparator
PATHWAY[1]	Phase II, double-blind, placebo-controlled, dose ranging RCT	Adults (aged 18-75 years) with inadequately controlled, severe asthma defined as: • Physician-diagnosed asthma for ≥12 months • Physician-prescribed asthma controller regimen with medium- or high-dose ICS plus LABA for ≥6 months • ACQ-6 score ≥1.5 at screening • ≥2 asthma exacerbation events or ≥1 severe asthma exacerbation resulting in hospitalisation within 12 months	Tezepelumab 70 mg SC Q4W + SoC (n=138) Tezepelumab 210 mg SC Q4W + SoC (n=137) Tezepelumab 280 mg SC Q2W + SoC (n=137)	Placebo SC Q2W + SoC (n=138)
NAVIGATOR[2]	Phase III, double-blind, placebo-controlled RCT	Adult and adolescents (aged 12-80 years) with uncontrolled severe asthma defined as: • Physician-diagnosed asthma for ≥12 months • Documented treatment with a total daily dose of either medium- or high-dose ICS for ≥3 months • Use of additional asthma controller medications for ≥3 months • ACQ-6 score ≥1.5 at screening • ≥2 asthma exacerbation events within 12 months	Tezepelumab 210 mg SC Q4W + SoC (n=528)	Placebo SC Q4W + SoC (n=531)
SOURCE[3]	Phase III double-blind, placebo-controlled RCT	Adults (aged 18-80 years) with severe, mOCS-dependent asthma defined as: • Physician-diagnosed asthma for ≥12 months • Physician-prescribed medium- or high-dose ICS as per GINA guidelines for ≥12 months • Physician-prescribed LABA and high-dose ICS for ≥3 months • mOCS for asthma for ≥6 months prior to Visit 1 and a stable dose of between ≥7.5 and ≤30 mg (prednisone or prednisolone) • ≥1 asthma exacerbation event within 12 months	Tezepelumab 210 mg SC Q4W plus ICS/LABA and mOCS + SoC (n=74)	Placebo SC Q4W plus ICS/LABA and mOCS + SoS (n=76)

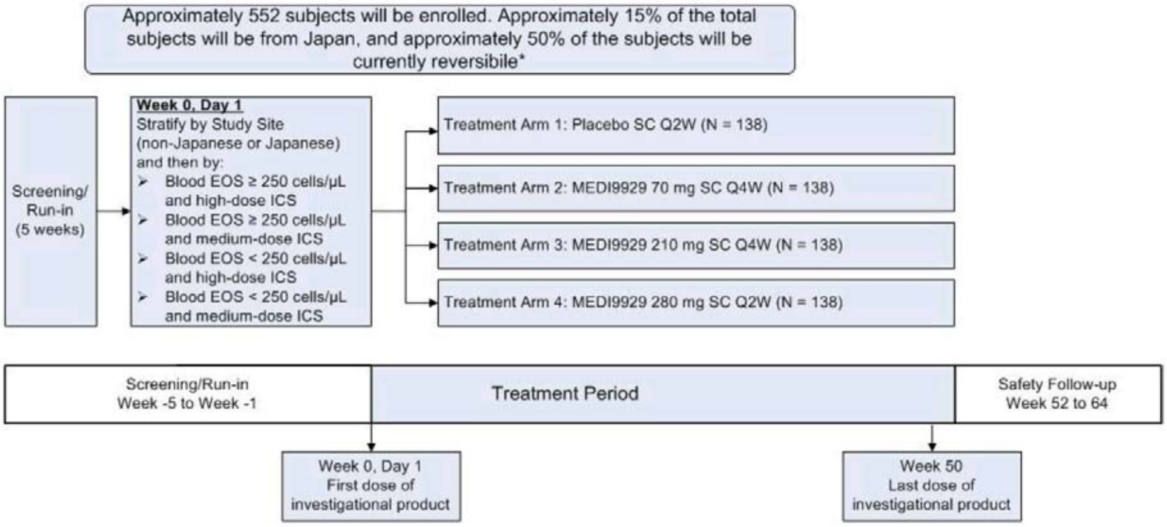
Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; mOCS, maintenance oral corticosteroids; RCT, randomized controlled trial; SC, subcutaneous; SoC, standard of care; Q4W, once every four weeks

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The company's primary evidence for tezepelumab comes from the Phase II study PATHWAY and the Phase III studies NAVIGATOR and SOURCE. The data from all three trials were used to inform the Company's economic model. Summary tables outlining the designs of the three studies are provided in the CS, Document B, Section B.2.3.1 Tables 9 and 10. The Company also provided schematics for the trials which are given in Figure 3, Figure 4, and Figure 5.

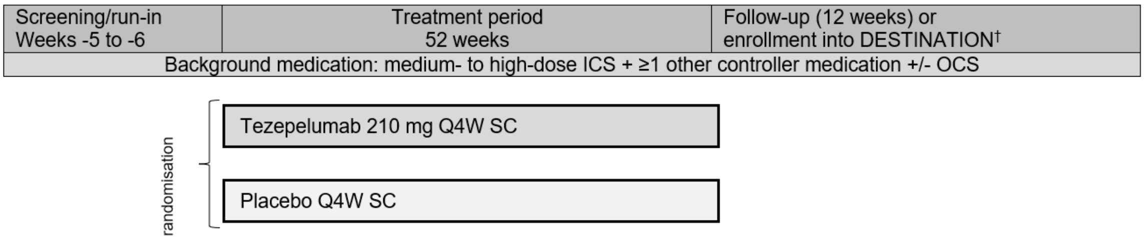
Figure 3: Schematic of PATHWAY trial design



Abbreviations: EOS, eosinophil; ICS, inhaled corticosteroid; MEDI9929, tezepelumab; Q4W, once every 4 weeks; SC, subcutaneous. * Current post-BD FEV1 reversibility was defined as post-BD change in FEV1 of ≥12% and ≥200 mL at one of the screening visits.

Source: CS, Figure 6, pp.59

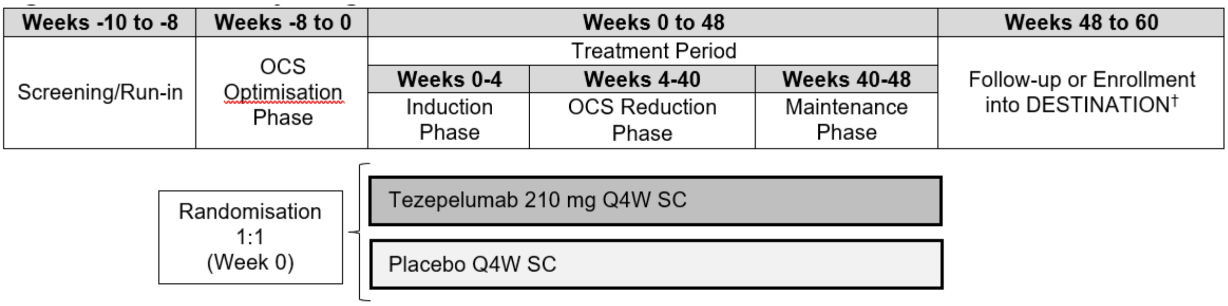
Figure 4: Schematic of NAVIGATOR trial design



Abbreviations: ICS, inhaled corticosteroid; OCS, oral corticosteroid; Q4W, once every 4 weeks; SC, subcutaneous. † DESTINATION is a long-term (1-year) extension study.

Source: CS, Figure 7, pp.60

Figure 5: Schematic of SOURCE trial design



Abbreviations: OCS, oral corticosteroid; Q4W, once every 4 weeks; SC, subcutaneous.
† DESTINATION is a long-term (1-year) extension study.
Source: CS, Figure 8, pp.60

PATHWAY, NAVIGATOR and SOURCE were all double-blind, placebo-controlled RCTs, and all provided a study arm where tezepelumab was given at 210 mg SC Q4W (subcutaneously at a dose of 210 mg once every four weeks). PATHWAY was a dosing study but did include a 210 mg SC Q4W dosing arm. Sample sizes in the relevant tezepelumab arms were N=138 in PATHWAY, N=528 in NAVIGATOR and N=74 in SOURCE, with similar sized placebo groups in each trial. Run in periods were 5 weeks in PATHWAY, 6 weeks in NAVIGATOR and two weeks in SOURCE. The EAG highlights that whilst PATHWAY and NAVIGATOR had 52-week treatment periods, SOURCE had a treatment period of 48 weeks. All three trials included a 12-week follow-up.

Data were provided for pre-planned subgroups based on biomarkers, participant characteristics and clinical characteristics as well as post-hoc subgroups in all three pivotal trials (see Section 3.2.3.1 for further details on subgroups). The design of the studies with regards to risk of bias (RoB) is discussed in CS, Document B, Section B.2.5 and critiqued in Section 3.2.2.6.

3.2.2.2. Population

In the three key pivotal trials (PATHWAY, NAVIGATOR and SOURCE), participants with severe uncontrolled asthma were recruited. The definition of severe uncontrolled asthma, and thus the inclusion criteria, varied between trials (see Table 8). Although the target condition in all three trials was fairly reasonably aligned with the NICE scope and the Company's decision problem, the EAG note the following differences:

- The decision problem specifies high dose ICS, but all three trials allowed the inclusion of participants using at least medium dose ICS. The proportion of participants using high dose

ICS at baseline was [redacted] in the relevant tezepelumab arm and [redacted] in the placebo arm in PATHWAY, [redacted] in the tezepelumab arm and [redacted] in the placebo arm in NAVIGATOR, and [redacted] in the tezepelumab arm and [redacted] in the placebo arm in SOURCE. The EAG highlight that the inclusion of participants using medium dose ICS risks the inclusion of under-treated participants who may be more likely to experience exacerbations. Subsequently, this may impact upon the effectiveness of the study drug in this population compared with the population in the decision problem (better response to treatment would be expected in participants with more exacerbations in the previous 12 months).

- PATHWAY and NAVIGATOR both allowed the inclusion of participants with at least two (rather than three) exacerbations, and SOURCE allowed the inclusion of participants with a single exacerbation, in the preceding 12 months. Additionally, PATHWAY allowed the inclusion of participants who had experienced any severe exacerbation resulting in hospitalisation in the preceding 12months. In PATHWAY, only [redacted] and [redacted] of those in the relevant tezepelumab and placebo arms respectively had experienced at least three exacerbations in the preceding 12 months. These figures were [redacted] and [redacted] respectively for NAVIGATOR and [redacted] and [redacted] for SOURCE (these data for SOURCE were calculated by the EAG using data in CS, Document B, Section B.2.3.3.3, Table 17).Whilst including participants with fewer than three exacerbations in the preceding 12 months is a pragmatic way to increase recruitment to the trials, these participants would be expected to be less likely to benefit from treatment than those specified in the decision problem.

Following examination of the other baseline characteristics of the three pivotal tezepelumab studies (provided in CS, Document B, Section B.2.3.3.1 to B.2.3.3.3, Tables 11 to 17), the EAG note that only NAVIGATOR included adolescents (those aged 12 to 80 years were eligible for inclusion). In NAVIGATOR, 82 of the 1,059 study participants (7.7%; [redacted]) were aged ≥12 to 17 years. PATHWAY and SOURCE included only adult participants (aged 18 to 75 years in PATHWAY and 18 to 80 years in SOURCE). Clinical expert advice to the EAG has suggested that, for this treatment and for this clinical population, adolescents aged at least 12 years can be assumed to be equivalent to the adult population. The paucity of data for adolescents should, therefore, not pose an issue.

The CS does not clearly specify how many participants were based at each site or in each country, but indicated in B.2.3.1 (Tables 9 and 10) that only NAVIGATOR included participants from the UK. Following clarification from the Company, it appears that no UK participants were recruited in NAVIGATOR. Therefore, no participants were included from England and Wales, the UK nations for which this appraisal is applicable. Following scrutiny of participant characteristics, clinical expert advice to the EAG indicated that, despite this, the included studies are likely to be generalisable to equivalent populations in England and Wales.

The EAG agree with the company that the participant characteristics in PATHWAY and NAVIGATOR were generally well balanced between the study groups. In SOURCE the groups were mostly well balanced. [redacted]

3.2.2.3. Intervention

The intervention in all three trials was tezepelumab 210 mg SC Q4W in addition to standard of care. As previously noted, PATHWAY was a dosing study and also included arms where tezepelumab was given SC at 70 mg Q4W and 280 mg Q2W, but it was the 210 mg SC Q4W that was of interest in this appraisal. In CS, Document B, Section B.2.3.1, Table 10, it is stated that the intervention in SOURCE was tezepelumab 210 mg SC Q4W plus ICS/LABA and mOCS in addition to standard of care. The EAG notes that ICS/LABA and mOCS were also given to the comparator group and could be considered part of standard of care.

3.2.2.4. Comparator

PATHWAY, NAVIGATOR and SOURCE all used a placebo control arm. As with the intervention arms, this was in addition to standard of care. The EAG highlight that, for PATHWAY, CS, Document B, Section B.2.3.1, Table 9 states that [redacted]. For NAVIGATOR and SOURCE, it was stated in CS, Document B, Section B.2.3.1, Tables 9 and 10, that [redacted]

3.2.2.5. Outcomes

The outcomes covered in the three pivotal tezepelumab studies were summarised in the CS section B.2.3.1, Table 9 (for PATHWAY and NAVIGATOR) and Table 10 (for SOURCE). The EAG considered the outcomes presented in the trials to generally encompass the outcomes from the NICE scope.

In the PATHWAY and NAVIGATOR trials the primary outcome was AAER (over 52 weeks), whereas in SOURCE, the primary outcome was categorised percent reduction in mOCS dose without loss of asthma control (over 48 weeks). In all three trials, exacerbation was defined as worsening of asthma leading to any of:

- A temporary bolus/burst of SCS (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening (a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day bolus/burst of SCS)
- An ED or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required SCS
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

A matrix of all primary and secondary outcomes in the three pivotal studies, alongside the location in the CS of the corresponding results, is provided in 3.2.3.1, Table 10.

3.2.2.6. Critical appraisal of the design of the studies

The Company provided risk of bias (RoB) assessments for PATHWAY, NAVIGATOR and SOURCE (in CS, Document B, Section B.2.5, Table 30) using the quality assessment checklist adapted from the University of York Centre for Reviews and Dissemination (CRD) guidance[35] for undertaking reviews in healthcare.

To ensure consistency with the methodological approach used to assess RoB in the other studies included in NMAs, and following a clarification request from the EAG, the Company also provided a RoB assessment for the three key tezepelumab trials using the NICE quality appraisal checklist for quantitative intervention studies (see Table 9).

Table 9: NICE quality appraisal checklist assessments for the tezepelumab trials

Questions	**NAVIGATOR (2020); NCT03347279**	**SOURCE (2020); NCT03406078**	**PATHWAY (2017); NCT02054130**
Section 1: Population			
1.1 Is the source population or source area well described?	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++
Section 2: Method of allocation to intervention (or comparison)*			
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++
2.3 Was the allocation concealed?	++	NA	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	++	+	+
2.6 Was contamination acceptably low?	+	+	++
2.7 Were other interventions similar in both groups?	++	+	++
2.8 Were all participants accounted for at study conclusion?	++	++	++
2.9.1 Did the setting reflect usual North American practice?	++	++	++
2.9.2 Did the setting reflect usual EU practice?	++	++	++
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NA
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	+	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	+	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA
Section 3: Outcomes			
3.1 Were outcome measures reliable?	++	++	++
3.2 Were all outcome measurements complete?	++	++	++
3.3 Were all important outcomes assessed?	++	++	++
3.4 Were outcomes relevant?	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++

Questions	**NAVIGATOR (2020); NCT03347279**	**SOURCE (2020); NCT03406078**	**PATHWAY (2017); NCT02054130**
3.6 Was follow-up time meaningful?	++	++	++
Section 4: Analyses			
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++
4.2 Was ITT analysis conducted?	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	+
4.4 Were the estimates of effect size given or calculable?	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	+	-
Section 5: Summary			
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom. *Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request. Source: Company clarification document, Table 1.

The EAG agree that both RoB evaluations (CS, Document B, Section B.2.5, Table 30, and Table 9) are generally consistent with each other, and that the trials are, overall, at low risk of bias. However, both tools only provided RoB assessment at the study level, and not at the outcome level. This was a reasonable approach, given the large number of outcomes (and the relatively large number of trials used in NMAs). However, the EAG note that there may not have been sufficient power to detect intervention effects across all included outcomes in all studies (and this was not assessed at the outcome level).

The EAG broadly agree with the study level ratings made for the three trials, in both the RoB assessments made using the quality assessment checklist adapted from the CRD guidance[35] (in CS, Document B, Section B.2.5, Table 30) and those made using the NICE quality appraisal checklist for quantitative intervention studies (in Table 9). The EAG note that, in NICE quality appraisal checklist assessment for SOURCE, allocation concealment was given as NR (not applicable; see Table 9). However, information in the CSR and in CS, Document B, Section B.2.5, Table 30 indicates that allocation concealment was both applicable and adequate in all three trials; use of [redacted] should have adequately ensured that allocation occurred without knowledge of which patient would receive which treatment.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Overview of the clinical effectiveness results

For PATHWAY, results for AAER were presented in CS Document B and secondary outcomes in CS Appendix L. For NAVIGATOR, AAER results and results from key secondary outcomes that informed the model (Pre-BD FEV_1, ACQ-6, AQLQ(S)+12, daily asthma symptom diary data, additional data on exacerbations and EQ-5D-5L) were provided in CS Document B, whereas results for secondary outcomes that did not inform the model were presented in CS Appendix M. For SOURCE, results for the primary outcome and key secondary outcomes (AAER results over 48 weeks, additional data on exacerbations, proportion with final OCS reduction, ASD, ACQ-6, AQLQ(S)+12, EQ-5D-5L) were provided in CS Document B. Results for secondary outcomes from SOURCE that did not inform the model were given in CS Appendix N.

In all three trials, data were provided for pre-planned subgroups as follows:

- **Biomarker subgroups** - FeNO (fraction of exhaled nitric oxide), blood eosinophil count, aeroallEAGen-specific IgE FEIA in all three pivotal trials, and additionally Th2 status in PATHWAY
- **Participant characteristics** – gender/sex and geographical region in all three pivotal trials, race in PATHWAY and NAVIGATOR, and age in NAVIGATOR and SOURCE
- **Clinical characteristics** - prior exacerbations and inhaled corticosteroid dose level in PATHWAY and NAVIGATOR, oral corticosteroid dose level and BMI in NAVIGATOR and SOURCE and nasal polyps in the 2 years prior and in NAVIGATOR

Post-hoc subgroup data were presented from NAVIGATOR for the following subgroups. With the exception of the dupilumab subgroup, data for these post-hoc subgroups were also presented from SOURCE:

- **Sum of all post-hoc subgroups** - populations aligned to current NICE-approved biologics for benralizumab, mepolizumab, omalizumab, and dupilumab plus the residual patients with 3 or more exacerbations or mOCS not currently eligible for biologic treatment)
- **Anti-IL-5 eligible post-hoc subgroup** - aligns with the NICE-recommended populations for benralizumab and mepolizumab which includes adult patients who have 300+ EOS (4+ Exacs OR mOCS) OR (400+ EOS AND 3 Exacs)
- **Dupilumab eligible post-hoc subgroup** - aligns with the NICE-recommended population for dupilumab which includes adult patients who have 4+ Exacs AND 150–299 EOS AND 25+ FeNO AND non-mOCS or adolescent patients (12–17 years who have 4+ Exacs AND 150+ EOS AND 25+ FeNO AND non-mOCS
- **Omalizumab eligible post-hoc subgroup** - aligns to the NICE-recommended population for omalizumab in the context of the tezepelumab licensed population which includes patients aged 12 years and over who have 30+ IgE AND (4+ Exacs OR mOCS)
- **Non-bio eligible (3+ exacerbations OR mOCS) post-hoc subgroup** - aligns to the residual 3 or more exacerbation or mOCS patient population who are not currently eligible for biologic treatment

Table 10 is a results matrix which illustrates, for each outcome, where the available data were presented in the CS for each trial and trial subgroup. In the sections that follow, the data across the trials and subgroups are collated by outcome.

Table 10: Clinical effectiveness results matrix for the pivotal trials (PATHWAY, NAVIGATOR and SOURCE)

	AAER[a]	**ACQ-6**	**CSE**[b]	**Medication**[c]	**DASD**	**Lung function**[d]	**HRQoL**[e]	**Adverse events**	**Other**
PATHWAY (whole sample)	CS B.2.6.1.1	CS L.2.7	CS L.2.1-L.2.5		CS L.2.9	CS L.2.6 (Pre-BD FEV_1)	CS L.2.8 (AQLQ(S)+12) CS L.2.10 (EQ-5D-5L)	CS B.2.10.1.1	
Pre-planned subgroups[f]	CS B.2.7.1.1								
NAVIGATOR (whole sample)	CS B.2.6.2.1	CS B.2.6.2.3	CS B.2.6.2.6	CS M.3.1 (rescue medication use)	CS B.2.6.2.5 CS M.3.1	CS B.2.6.2.2 (Pre-BD FEV_1) CS M.3.2 (PEF and $FEF_{25–75\%}$)	CS B.2.6.2.4 (AQLQ(S)+12) CS B.2.6.2.6 (EQ-5D-5L)	CS B.2.10.1.2	CS M.3.5 (resource utilisation) CS M.3.3 (SGRQ) CS M.3.4 (PGI-C, PGI-S, CGI-C)
Pre-planned subgroups[g]	CS B.2.7.1.2								
Post-hoc subgroups[h]	CS B 2.7.2.1	CS B 2.7.2.1				CS B 2.7.2.1 (Pre-BD FEV_1)			
SOURCE (whole sample)	CS B.2.6.3.2	CS B.2.6.3.3	CS B.2.6.3.3	CS B.2.6.3.1 and CS B.2.6.3.3 (OCS reduction) CS N.3.2 – N.3.3 (rescue medication use)	CS B.2.6.3.3	CS N.3.1 (Pre-BD FEV_1)) CS M.3.4 (PEF)	CS B.2.6.3.3 (AQLQ(S)+12; EQ-5D-5L)	CS B.2.10.1.3	CS B.2.6.3.3 (resource utilisation)

	AAER[a]	ACQ-6	CSE[b]	Medication[c]	DASD	Lung function[d]	HRQoL[e]	Adverse events	Other
Pre-planned subgroups [i]				CS B.2.7.1.3 (% OCS reduction)					
Post-hoc subgroups[j]	CS B.2.7.2.2	CS B.2.7.2.2				CS B.2.7.2.2 (Pre-BD FEV_1)			

Key: AAER Annualised Asthma Exacerbation Rate; ACQ-6 Asthma control questionnaire 6-item; CGI-C Clinician Global Impression of Change; CS Company submission; CSE Clinically significant exacerbations; DASD Daily Asthma Symptom Diary; ED, emergency department; FEF25–75%, forced expiratory flow over 25–75% of the vital capacity; mCOS maintenance corticosteroids; PEF Peak expiratory flow; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; SGRQ St George's respiratory questionnaire

Notes: [a] At 52 weeks in PATHWAY and NAVIGATOR, at 48 weeks in SOURCE; [b] Includes time to first asthma exacerbation, proportion experiencing no asthma exacerbations, and AAER associated with ED visit or hospitalisation in all three studies and time to first exacerbation associated with ED visit or hospitalisation in PATHWAY and SOURCE; [c] Includes reduction in OCS dose, proportion with a reduction in final dose, rescue medication use; [d] Includes Pre-BD FEV_1, PEF and FEF; [e] Includes EQ-5D-5L and AQLQ(S)+12; [f] Pre-planned subgroups in PATHWAY were gender, race, FeNO (fraction of exhaled nitric oxide), blood eosinophil count, FEIA (fluorescent enzyme immunoassay), Th2 status, prior exacerbations, geographical region, and inhaled corticosteroid dose level; [g] Pre-planned subgroups in NAVIGATOR were biomarker subgroups (blood eosinophil count, aeroallEAGen-specific IgE FEIA, FeNO), baseline characteristics (inhaled and oral corticosteroid doses, age, gender, race, exacerbations in the year prior, BMI, geographical region, nasal polyps in the 2 years prior); [h] Post-hoc subgroups in NAVIGATOR were the sum of post-hoc subgroups, the anti-IL-5 eligible subgroup, the dupilumab eligible subgroup, the omalizumab eligible subgroup, and the non-bio eligible (3+ exacerbations OR mOCS) subgroup; [i] Pre-planned subgroups in SOURCE were biomarker subgroups (blood eosinophil count, aeroallEAGen-specific IgE FEIA, FeNO) and baseline characteristics (baseline oral corticosteroid dose, age, sex, BMI, geographical region); [j]Post-hoc subgroups in SOURCE were the sum of post-hoc subgroups, the anti-IL-5 eligible subgroup, the omalizumab eligible subgroup, and the non-bio eligible (3+ exacerbations OR mOCS) subgroup

Annualised Asthma Exacerbation Rate (AAER)

Annualised Asthma Exacerbation Rate (AAER) was the primary outcome in PATHWAY and NAVIGATOR (over 52 weeks) and was also reported as a secondary outcome in SOURCE (over 48 weeks).

Whole study data (by study arm) are given in CS, Document B, Section B.2.6.1.1, Table 31 for PATHWAY, CS, Document B, Section B.2.6.2.1, Table 32 for NAVIGATOR and CS, Document B, Section B.2.6.3.2, Table 44 for SOURCE. For brevity, and to better consolidate the data across the trials, the EAG has combined key information for this outcome in Table 11. The EAG note that the data provided by the Company for PATHWAY were based on the ITT sample, but the data provided for NAVIGATOR and SOURCE were based on the full analysis set (FAS). The EAG confirm that the definitions of ITT for PATHWAY and FAS for NAVIGATOR and SOURCE are reasonably aligned (all randomised participants who received at least one dose of study medication as assigned).

Table 11: AAER in PATHWAY (ITT), NAVIGATOR (FAS) and SOURCE (FAS)

	PATHWAY		**NAVIGATOR**		**SOURCE**	
	210 mg Q4W (n=137)	**Placebo (n=138)**	**Tezepelumab (n=528)**	**Placebo (n=531)**	**Tezepelumab [redacted]**	**Placebo [redacted]**
AAER (95% CI)	0.20 (0.13, 0.30)	0.72 (0.59, 0.88)	0.93 (0.80, 1.07)	2.10 (1.84, 2.39)	[redacted]	[redacted]
Rate ratio (95% CI)	0.29 (0.16, 0.51)	-	0.44 (0.37, 0.53)	-	[redacted]	
p-value	<0.001	-	<0.001		[redacted]	

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set; ICS, inhaled corticosteroids; ITT, intent-to-treat; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

Source: Adapted from CS, Document B, Section B.2.6, Tables 31, 32 and 44

In PATHWAY and SOURCE, treatment with tezepelumab 210 mg SC Q4W resulted in a statistically significant (p<0.001) reduction in the rate of asthma exacerbations over 52 weeks compared with placebo (rate ratio 0.29 (95% CI 0.16, 0.51) in PATHWAY, rate ratio 0.44 (95% CI 0.37, 0.53) in NAVIGATOR. In SOURCE

[redacted]

[redacted]*AAER for pre-planned sub*groups

As can be seen from Table 7, AAER data were provided for pre-planned subgroups in PATHWAY (CS, Document B, Section B.2.7.1.1) and NAVIGATOR (CS, Document B, Section B.2.7.1.2). Figure 6 shows that, for AAER at 52 weeks, tezepelumab was favoured over placebo for all pre-planned subgroups in PATHWAY.

Figure 6: AAER over 52 weeks by pre-planned subgroups (ITT) in PATHWAY

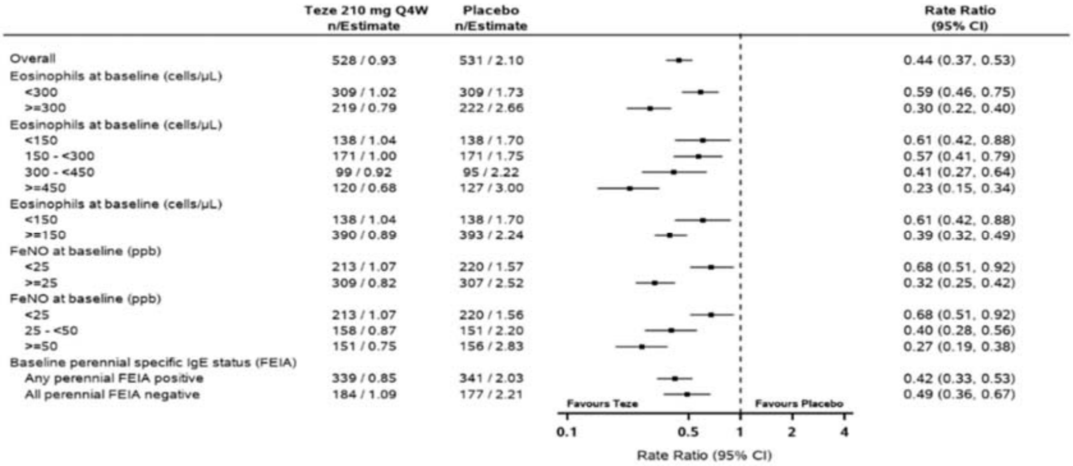
[redacted]

Abbreviations: AERR, asthma exacerbation rate reduction; CI, confidence interval; FEIA, fluorescent enzyme immunoassay; FeNO. fraction of exhaled nitric oxide; ICS, inhaled corticosteroids; ITT, intent-to-treat; MEDI9929, tezepelumab; ppb, parts per billion; Q4W, once every 4 weeks.

Source: CS, Document B, Section B.2.7.1.1, Figure 23

Similarly, in NAVIGATOR, all pre-planned subgroup analyses for AAER based on biomarkers (Figure 7) and most subgroup analyses for AAER based on baseline characteristics (Figure 8) favoured tezepelumab over placebo.

Figure 7: AAER ratio over 52 weeks by baseline biomarker subgroup (FAS)



	Teze 210 mg Q4W n/Estimate	Placebo n/Estimate	Rate Ratio (95% CI)
Overall	528 / 0.93	531 / 2.10	0.44 (0.37, 0.53)
Eosinophils at baseline (cells/µL)			
<300	309 / 1.02	309 / 1.73	0.59 (0.46, 0.75)
>=300	219 / 0.79	222 / 2.66	0.30 (0.22, 0.40)
Eosinophils at baseline (cells/µL)			
<150	138 / 1.04	138 / 1.70	0.61 (0.42, 0.88)
150 - <300	171 / 1.00	171 / 1.75	0.57 (0.41, 0.79)
300 - <450	99 / 0.92	95 / 2.22	0.41 (0.27, 0.64)
>=450	120 / 0.68	127 / 3.00	0.23 (0.15, 0.34)
Eosinophils at baseline (cells/µL)			
<150	138 / 1.04	138 / 1.70	0.61 (0.42, 0.88)
>=150	390 / 0.89	393 / 2.24	0.39 (0.32, 0.49)
FeNO at baseline (ppb)			
<25	213 / 1.07	220 / 1.57	0.68 (0.51, 0.92)
>=25	309 / 0.82	307 / 2.52	0.32 (0.25, 0.42)
FeNO at baseline (ppb)			
<25	213 / 1.07	220 / 1.56	0.68 (0.51, 0.92)
25 - <50	158 / 0.87	151 / 2.20	0.40 (0.28, 0.56)
>=50	151 / 0.75	156 / 2.83	0.27 (0.19, 0.38)
Baseline perennial specific IgE status (FEIA)			
Any perennial FEIA positive	339 / 0.85	341 / 2.03	0.42 (0.33, 0.53)
All perennial FEIA negative	184 / 1.09	177 / 2.21	0.49 (0.36, 0.67)

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; teze, tezepelumab; Q4W, once every 4 weeks

Rate ratio is displayed on the log scale. The dotted line represents no treatment difference. Model, including subgroups, was a negative binomial regression analysis with treatment, region, age, history of exacerbations, subgroup (if not already included), and treatment * subgroup as covariates. Time at risk was used as an offset variable in the model to adjust for subjects' having different exposure times during which the events occur. Source: CS, Document B, Section B.2.7.1.2, Figure 24

However, for adolescents, those of Black or African American or "Other" race, those using OCS at baseline, participants from Central/Eastern Europe and those with [redacted], AAER results indicated no statistically significant difference between tezepelumab and placebo (Figure 8). The EAG agree that is plausible, but not necessarily the case, that this was due to the small sample sizes for these subgroups.

Figure 8: AAER ratio over 52 weeks by baseline characteristic subgroup (FAS)

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set; ICS, inhaled corticosteroid; OCS, oral corticosteroid; teze, tezepelumab; Q4W, once every 4 weeks. Rate ratio is displayed on the log scale. The dotted line represents no treatment difference. Model, including subgroups, was a negative binomial regression analysis with treatment, region, age, history of exacerbations, subgroup (if not already included), and treatment * subgroup as covariates. Time at risk was used as an offset variable in the model to adjust for subjects' having different exposure times during which the events occur. Source: CS, Document B, Section B.2.7.1.2, Figure 25

AAER for post-hoc subgroups

As can be seen from Table 10, AAER data were provided for post-hoc subgroups in NAVIGATOR and SOURCE. These post-hoc subgroup analyses were used to inform the economic model.

AAER data were presented for the following post-hoc subgroups: sum of all post hoc subgroups (CS, Document B, Section B. 2.7.2.1, Table 49 for NAVIGATOR; CS, Document B, Section B.2.7.2.2, Table 69 for SOURCE), Anti-IL-5 eligible subgroup (CS, Document B, Section B. 2.7.2.1, Table 53 for NAVIGATOR; CS, Document B, Section B.2.7.2.2, Table 73 for SOURCE), dupilumab eligible subgroup (CS, Document B, Section B. 2.7.2.1, Table 57 for NAVIGATOR; not applicable for SOURCE), omalizumab eligible subgroup (CS, Document B, Section B. 2.7.2.1, Table 61 for NAVIGATOR; CS, Document B, Section B.2.7.2.2, Table 77 for SOURCE) and the non-bio eligible subgroup (CS, Document B, Section B. 2.7.2.1, Table 65 for NAVIGATOR; CS, Document B, Section B.2.7.2.2, Table 81 for SOURCE).

To improve clarity, the EAG has consolidated the data from the relevant tables into single tables for NAVIGATOR (Table 12) and SOURCE (Table 13). As can be seen from Table 12, tezepelumab 210 mg SC Q4W resulted in a statistically significant reduction in the rate of asthma exacerbations over 52 weeks compared with placebo for all but the dupilumab eligible subgroup in NAVIGATOR. Table 13 shows that, in SOURCE, tezepelumab 210 mg SC Q4W only resulted in a statistically significant reduction in the rate of asthma exacerbations over 48 weeks compared with placebo for the anti-IL-5 eligible subgroup.

Table 12: Post-hoc subgroup analyses from NAVIGATOR (AAER ratio over 52 weeks, negative binomial model; FAS)

	Sum of all post-hoc subgroups		Anti-IL-5 eligible subgroup		Dupilumab eligible subgroup		Omalizumab eligible subgroup		Non-bio eligible subgroup	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set, IL, interleukin.
A rate ratio <1 favoured tezepelumab. A negative binomial regression analysis with treatment, region, age group, and history of exacerbations as covariates. The logarithm of the time at risk was used as an offset variable. Annual exacerbation rates and absolute differences displayed were estimated marginal rates from the model. Absolute difference was the difference between the marginal rates. Annual exacerbation rates displayed were estimated marginal rates from the model. Absolute difference was the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences were estimated via the delta method.

Source: Adapted from Tables 49, 53, 57, 61 and 65, CS, Document B, Section B. 2.7.2.1

Table 13: Post-hoc subgroup analyses from SOURCE (AAER ratio over 48 weeks, negative binomial model; FAS)

	Sum of all post-hoc subgroups		Anti-IL-5 eligible subgroup		Omalizumab eligible subgroup		Non-bio eligible subgroup	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set, IL, interleukin.
A rate ratio <1 favoured tezepelumab. A negative binomial regression analysis with treatment, region, age group, and history of exacerbations as covariates. The logarithm of the time at risk was used as an offset variable. Annual exacerbation rates and absolute differences displayed were estimated marginal rates from the model. Absolute difference was the difference between the marginal rates. Annual exacerbation rates displayed were estimated marginal rates from the model. Absolute difference was the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences were estimated via the delta method. Source: Adapted from Tables 69, 73, 77 and 81, CS, Document B, Section B.2.7

Annualised severe asthma exacerbation rate (related to hospitalisations/ED visits)

Data on annualised severe asthma exacerbation rates (AER; i.e. exacerbations associated with ED visits or hospitalisation) were reported for all three key tezepelumab studies (CS, Document B, Section B.2.6.2.6, Table 40 for NAVIGATOR, CS L 2.3, Table 52 for PATHWAY and CS, Document B, Section B.2.6.3.3, Table 45 for SOURCE). Data were across 52 weeks for PATHWAY and NAVIGATOR and across 48 weeks for SOURCE. For clarity, the EAG has consolidated the key data on annualised severe AER from the three tezepelumab studies into Table 14.

Table 14: Annualised severe AER in PATHWAY, NAVIGATOR and SOURCE

	NAVIGATOR		PATHWAY		SOURCE	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]	

[redacted]. Source: Adapted from Table 40, CS, Document B, Section B.2.6.2.6, Table 45, CS, Document B, Section B.2.6.3.3 and Table 52, CS L 2.3

As can be seen in Table 14, annualised severe AERs [redacted] In SOURCE, a similar pattern of results was found [redacted]

Additional data on clinically significant exacerbations

Aside from annualised rates of exacerbations/severe exacerbations, the Company reported additional data on clinically significant exacerbations from PATHWAY (CS L.2.1, 2.2, 2.4 and 2.5), NAVIGATOR (CS, Document B, Section B.2.6.2.6) and SOURCE (CS, Document B, Section B.2.6.3.3). No subgroup data from any of the pivotal tezepelumab trials were available for these outcomes.

Time to first asthma exacerbation

In NAVIGATOR, the time to first exacerbation was statistically significantly longer in the tezepelumab versus the placebo arm (HR=0.59, 95% CI 0.50, 0.70, p<0.001). This was shown in CS, Document B, Section B.2.6.2.6, Figure 17. [redacted].

In PATHWAY, time to severe exacerbation was [redacted]This was shown in CS L.2.4, Figure 115. The EAG note that severe exacerbations in CS L.2.4 for PATHWAY. In SOURCE, between-group analysis comparing time to severe exacerbation associated with hospitalisation/ED visit [redacted] (CS, Document B, Section B.2.6.3.3, Figure 22).

Proportion of subjects experiencing asthma exacerbations

CS, Document B, Section B.2.6.2.6 reports that, in NAVIGATOR, a [redacted]). In PATHWAY, [redacted] over the 52 week study period (CS L.2.2, Table 51). It is unclear why the proportion of participants experiencing no exacerbations over 52 weeks was higher in PATHWAY than in NAVIGATOR. In SOURCE, a numerically higher proportion of subjects in the tezepelumab arm did not experience an asthma exacerbation between baseline and 48 weeks compared with placebo , but this did not reach statistical significance (47.3% versus 34.2%, OR=1.68, 95% CI, 0.85, 3.31, p=0.133).

In PATHWAY, it was also reported that the proportion of participants experiencing ≥1 asthma exacerbation over 52 weeks [redacted]; CS L.2.2). Similarly, CS L.2.5 states that [redacted]Again, severe exacerbations were not explicitly defined in the CS L.2.5.

Reduction in daily mOCS dose

In SOURCE, the primary outcome was categorised percent reduction in daily mOCS dose (at week 48, without loss of asthma control). PATHWAY and NAVIGATOR did not contribute to data on mOCS dose reduction. For SOURCE, full analysis set data for this outcome were reported in CS, Document B, Section B.2.6.3.1. Categories were: reduction from baseline of ≥90 to ≤100%, ≥75 to <90%, ≥50 to <75%, >0 to <50% and no reduction/any increase. It may have been more clinically meaningful to use the following categories <50% reduction (or increase), ≥50 to <75% reduction and ≥75 reduction. Data were presented in CS, Document B, Section

B.2.6.3.1, Figure 18 and Table 42. The odds of reaching a category with a greater percent mOCS reduction with tezepelumab compared with placebo was 1.28 (95% CI: 0.69, 2.35) and this did not reach statistical significance (p=0.434).

CS, Document B, Section B.2.6.3.3, Table 46 provided further data from SOURCE on mOCS reduction from baseline, but none of the analyses demonstrated a statistically significant difference between the tezepelumab and placebo arms. This included outcomes that clinical expert advice to the EAG indicated were clinically meaningful: proportion of participants achieving 100% reduction (OR= 1.35, 95% CI 0.68, 2.68, p=0.385), proportion achieving ≥50% reduction (OR= 1.24, 95% CI 0.60, 2.57, p=0.559), final daily dose ≥5mg (OR= 0.88, 95% CI 0.40, 1.94, p=0.745).

The mean and median change from baseline in daily mOCS dose over time in SOURCE were also presented (in CS, Document B, Section B.2.6.3.1, Figures 19 and 20 respectively). The median difference in percentage reduction from baseline in mOCS was reported [redacted]

***Reduction in daily mOCS dose for* pre-planned subgroups**

The CS reports that [redacted] on the primary outcome (percent reduction in daily mOCS dose; CS, Document B, Section B.2.7.1.3). Figure 9 shows that odds ratio point estimates [redacted] The Company also state that [redacted]). The EAG largely agree with this, but note that the confidence intervals cross 1. The EAG agree with the Company that, due to small subgroup sample sizes, these results should be interpreted with caution.[redacted]

Figure 9: Categorised percent reduction in daily OCS dose at Week 48 by baseline characteristic subgroup (FAS)

[redacted]

Abbreviations: AI, adrenal insufficiency; BMI, body mass index; CI, confidence interval; FAS, full analysis set; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroid; ppb, parts per billion; Q4W, once every 4 weeks; Teze, tezepelumab.
Cumulative odds ratio is presented on the log scale. Dotted line represents no treatment difference. Derivation of OCS dose included a therapy reason of "Asthma maintenance dose", "Titration, due to asthma", and "Other: AI".
Model: a proportional odds model with treatment group, region, OCS dose at baseline, subgroup (if not already included) and treatment * subgroup as covariates.

Source: Figure 26, CS, Document B, Section B.2.7.1.3.

Rescue medication

Rescue medication use was provided in CS, [redacted] (refer to CS Appendix N.3.2 – N.3.3 for SOURCE and CS Appendix M.3.1 for NAVIGATOR). PATHWAY did not contribute to the data for this outcome. Data on rescue medication use was not provided for any subgroups.

Asthma Control Questionnaire 6-item (ACQ-6)

Data from the Asthma Control Questionnaire 6-item (ACQ-6) were provided from all three pivotal tezepelumab studies. Whole study data (by study arm) were given in CS L.2.7, Tables 54 and 55 for PATHWAY, CS, Document B, Section B.2.6.2.3, Tables 34 and 35 for NAVIGATOR, and CS, Document B, Section B.2.6.3.3 (in text only) for SOURCE. Again, data from PATHWAY and NAVIGATOR were based on a 52-week treatment period, whereas data from SOURCE were based on a 48 week treatment period. The EAG highlights that, in PATHWAY, the company state that [redacted] The EAG agree with the company that [redacted]

The EAG has consolidated key data on change in ACQ-6 scores from baseline in Table 15 (note that, for PATHWAY, only 52 week data, and only data from the tezepelumab 210 mg Q4W and placebo arms have been consolidated). In all three studies, improvement from baseline in ACQ-6 scores was greater for the relevant tezepelumab arm than for the placebo arm. Graphical representation of adjusted mean change in ACQ-6 scores from baseline for the three studies can be found in CS L.2.7, Figure 117 for PATHWAY and CS, Document B, Section B.2.6.2.3, Figure 14 for NAVIGATOR (not provided for SOURCE).

All three key tezepelumab studies also provided data on the proportion of participants who had a change in baseline ACQ-6 score ≥0.5 (in CS, Document B, Section B.2.6.2.3, Table 35 for

NAVIGATOR, CS L.2.7 Table 55 for PATHWAY and in the text (CS, Document B, Section B.2.6.3.3) for SOURCE). In PATHWAY, it was stated that LOCF was used to deal with missing data and the EAG note that the number of missing data appears low in CS L.2.7, Table 55, even though fewer ACQ-6 data appeared to be available at 52 weeks in CS L.2.7, Table 54. The reasons for this are unclear. The EAG has consolidated the ACQ-6 change from baseline ≥0.5 data from the three tezepelumab studies in Table 16 and agree with the company that in all three trials these data favour tezepelumab 210 mg Q4W over placebo.

Table 15: ACQ-6 score change from baseline in PATHWAY (ITT), NAVIGATOR (FAS) and SOURCE (FAS)

	PATHWAY (52 weeks)		NAVIGATOR (52 weeks)		SOURCE (48 weeks)	
	[redacted]	[redacted]	Tezepelumab (n=528)	Placebo (n=531)	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
LS mean difference (95% CI)	[redacted]		–0.33 (–0.46, –0.20)		–0.37 (–0.71, –0.02)	
p-value	[redacted]		<0.001		NR	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CI, confidence interval; FAS, full analysis set; ITT, intention-to-treat; LS, least squares; NR, not reported

The ACQ-6 score was computed as the unweighted mean of the responses to the six questions. If response to any of the questions was missing, the ACQ-6 was missing. Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. Calculation of percentages was based on the number of subjects in the FAS with a completed assessment at each time point. The estimate of the odds ratio was obtained using a GEE model for repeated measures binary data with unstructured covariance structure and treatment, region, age, visit, visit * treatment, and baseline ACQ-6 score as covariates. Unadjusted CI and nominal p-values are presented, as the analysis was not included in the multiple testing procedure.

Source: Adapted from Tables 34 and 35, CS, Document B, Section B.2.6.2.3 and Table 54, CS L.2.7 with the addition of data from text in CS, Document B, Section B.2.6.3.3

Table 16: ACQ-6 change from baseline ≥0.5 in PATHWAY (ITT), NAVIGATOR (FAS) and SOURCE (FAS)

	PATHWAY (52 weeks)		NAVIGATOR (52 weeks)		SOURCE (48 weeks)	
	[redacted]	[redacted]	Tezepelumab	Placebo	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

	PATHWAY (52 weeks)		NAVIGATOR (52 weeks)		SOURCE (48 weeks)	
	[redacted]	[redacted]	**Tezepelumab**	**Placebo**	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR (65.2)	NR (45.6)
OR (95% CI)	NR		[redacted]		[redacted]	
p-value	[redacted]		[redacted]		[redacted]	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CI, confidence interval; FAS, full analysis set; NR, not reported; OR, odds ratio.

Source: Adapted from Table 35, CS, Document B, Section B.2.6.2.3 and Table 55, CS L.2.7 with the addition of data from text in CS, Document B, Section B.2.6.3.3.

Based on ACQ-6 data, asthma control at treatment end-point was also reported for PATHWAY and SOURCE. Similar data from NAVIGATOR were not available in either the CS or CSR, despite the fact that ACQ-6 asthma control cut-offs were defined in all three CSRs (mean scores of ≤0.75 for adequately controlled asthma, scores between 0.75 and <1.5 for partially controlled asthma, and a score of ≥1.5 for asthma that was not well controlled). For SOURCE, the CS reported that more patients in the tezepelumab group achieved asthma control (ACQ ≤0.75) at 48 weeks compared with placebo (30.3 versus 14.7%). In PATHWAY CS L.2.7, Table 55, it was reported that more patients in the tezepelumab group achieved asthma control (ACQ-6 ≤0.75) at 52 weeks when compared with placebo (26.7 versus 16.0%).

Change from baseline in ACQ-6 for post-hoc subgroups

For both NAVIGATOR and SOURCE, ACQ-6 data were only presented for the post-hoc subgroups (in CS, Document B, Section B. 2.7.2.1, Tables 51, 55, 59, 63 and 67 for NAVIGATOR and CS, Document B, Section B.2.7.2.2, Tables 71, 75, 79 and 83 for SOURCE). The EAG note that ACQ-6 data for pre-planned subgroups are available in the CSR for NAVIGATOR. There were no ACQ-6 subgroup data available from PATHWAY. For clarity, the EAG has consolidated these data (Table 17 for NAVIGATOR and Table 18 for SOURCE).

Table 17: CFB to Week 52 in ACQ-6 for NAVIGATOR post-hoc subgroups (MMRM, FAS)

	Sum of all post-hoc subgroups		Anti-IL-5 eligible subgroup		Dupilumab eligible subgroup		Omalizumab eligible subgroup		Non-bio eligible subgroup	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; mOCS, maintenance oral corticosteroid treatment.

The model with unstructured covariance structure was: CFB in ACQ-6 = treatment group + region + age + baseline ACQ-6 + visit + treatment * visit. Subjects with data at baseline and at least one post-baseline time point were included in the analysis. n1 = number of subjects contributing to the analysis (i.e. the number of subjects with at least one CFB value at any post baseline visit). n2 = number of subjects with a CFB value at each timepoint.

Source: Adapted from Tables 51, 55, 59, 63 and 67, CS, Document B, Section B. 2.7.2.1

Table 18: CFB to Week 48 in ACQ-6 for SOURCE post-hoc subgroups (MMRM, FAS)

	Sum of all post-hoc subgroups		Anti-IL-5 eligible subgroup		Omalizumab eligible subgroup		Non-bio eligible subgroup	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures. Baseline is defined as the last non-missing measurement recorded on or prior to randomisation. The ACQ-6 score is computed as the unweighted mean of the responses to the 6 questions. If response to any of the questions is missing, the ACQ-6 will be missing. Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in ACQ-6 = Treatment group + region + baseline ACQ-6 + visit + treatment * visit. Subjects with data at baseline and at least at one post-baseline time point included in analysis.

Source: Adapted from Tables 71, 75, 79 and 83, CS, Document B, Section B.2.7.2.2

Daily asthma symptom diary

All three pivotal tezepelumab trials provided data on asthma symptom diary (ASD) scores. Change from baseline to 52 weeks in ASD data from PATHWAY were presented in CS Appendix L.2.9, Table 58, where [redacted] A statistically significant between-group difference in this outcome, favouring tezepelumab over placebo, was found in NAVIGATOR (presented in CS, Document B, Section B.2.6.2.5, Table 38; –0.70 versus –0.59, respectively; LS mean difference –0.11, 95% CI –0.19, –0.04, p=0.004). The ASD data from SOURCE were presented in text (CS, Document B, Section B.2.6.3.3). The between-group difference in change from baseline to 48 weeks in these data did not appear to reach statistical significance (LS mean difference –0.10, 95% CI –0.29, 0.09). The EAG have consolidated these data, across trials, in Table 19.

Table 19: ASD score change from baseline in PATHWAY, NAVIGATOR and SOURCE

	PATHWAY		**NAVIGATOR**		**SOURCE**	
	[redacted]	[redacted]	**Tezepelumab (n=528)**	**Placebo (n=531)**	**Tezepelumab (n=74)**	**Placebo (n=76)**
n	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
LS mean difference (95% CI)	[redacted]		[redacted]		–0.10 (–0.29, 0.09)	
p-value	[redacted]		[redacted]		NR	

Abbreviations: ASD, Asthma Symptom Diary; CI, confidence interval; FAS, full analysis set; LS, least squares; NR, not reported. Source: Adapted from CS Table 58, Appendix L.2.9; CS Table 38, B.2.6.2.5; and CS, Document B, Section B.2.6.3.3

CS Table 39 and CS Figure 16 also provided data on responders from NAVIGATOR (responders were defined as those with a change from baseline in ASD scores ≥0.5). By this definition [redacted]. It was reported in CS, Document B, Section B.2.6.3.3 that, in SOURCE, more participants experienced a clinically meaningful improvement in ASD score from baseline to Week 48 with tezepelumab compared with placebo (43.1 vs 29.4% respectively, OR: 8.98, 95% CI 0.63, 127.41). The EAG again highlight the wide confidence intervals and the small sample sizes in SOURCE. Similar data were not available for PATHWAY.

Data on the weekly percentage of symptomatic days as measured by the ASD were reported in CS M.3.1 for [redacted]. CS, Document B, Section B.2.6.3.3 reported that, in SOURCE, there were fewer symptomatic days in the tezepelumab arm versus the placebo arm over 48 weeks (change from baseline –27.94 versus –6.60, respectively). It was not made clear over what timeframe the data were collected at baseline and the study endpoint. Similar data were not available for PATHWAY.

The EAG note that although no ASD data were provided in the CS for any subgroups, subgroup data are available in the CSR for NAVIGATOR. Based on the data presented in the NAVIGATOR CSR, the EAG highlight that [redacted]

Pulmonary function (pre-BD FEV_1, $FEF_{25–75\%}$ and PEF)

All three trials provided data on pre-BD FEV_1 (in CS, Appendix L, Section L.2.6, Table 53 and Figure 116 for PATHWAY; CS, Document B, Section B.2.6.2.2, Table 33 and Figure 13 for NAVIGATOR; CS, Appendix N, Appendix N.3.1, Figure 120 for SOURCE).

Table 20: pre-BD FEV1 change from baseline for PATHWAY, NAVIGATOR and SOURCE

	PATHWAY		**NAVIGATOR**		**SOURCE**	
	[redacted]	[redacted]	**Tezepelumab (n=528)**	**Placebo (n=531)**	[redacted]	[redacted]
n1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline (L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]		[redacted]		[redacted]	
p-value	[redacted]		[redacted]		[redacted]	

Abbreviations: BD, bronchodilator; CI, confidence interval; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; LS, least squares; n1, number of subjects contributing to the analysis, i.e. the number of subjects with at least one change from baseline value at any post baseline visit, n2, number of subjects with a change from baseline value at each timepoint.

Source: Adapted from Table 53, CS Appendix L, Section L.2.6; Table 33, CS, Document B, Section B.2.6.2.2 and CS Appendix N, Section N.3.1.

The data from [redacted]; 0.23 L versus 0.10 L, LS mean difference 0.13 L, 95% CI 0.08, 0.18, p<0.001 for NAVIGATOR; [redacted] The EAG has consolidated these data in Table 20.

Post-hoc subgroup data from NAVIGATOR and SOURCE were also available for pre-BD FEV_1 (in CS, Document B, Section B. 2.7.2.1, Tables 50, 54, 58, 62 and 66 for NAVIGATOR and CS, Document B, Section B.2.7.2.2, Tables 70, 74, 78 and 82 for SOURCE). Again, data from SOURCE did not include a dupilumab eligible post-hoc subgroup. For clarity, the EAG has consolidated these post-hoc subgroup data into Table 21 (data from NAVIGATOR) and Table 22 (data from SOURCE). The EAG note that pre-BD FEV_1 data were available for the pre-planned subgroups in the trial CSRs, but these were not reported in the CS. The EAG highlight that in the NAVIGATOR CSR it was reported that tezepelumab did not statistically significantly improve pre-BD FEV_1 compared with placebo for the following pre-planned subgroups: eosinophil level <150 cells/µL, treatment with medium-dose ICS at baseline, adolescents, adults aged ≥65, Black or African American race, “Other” race, BMI ≥30, BMI <18.5, and geographical locations of South America, Central and Eastern Europe, and Western Europe and Australia.

The Company also provided data from NAVIGATOR on $FEF_{25–75\%}$ (CS, Appendix M, Appendix M.3.2) and from NAVIGATOR and SOURCE on PEF (CS, Appendix M, Appendix M.3.2 and CS Appendix N, Section N.3.4 respectively). In NAVIGATOR there was a greater improvement from [redacted] Table 23 summarises the remaining PEF and $FEF_{25–75\%}$ data reported in the CS.

Table 21: CFB to Week 52 in pre-BD FEV$_1$: NAVIGATOR post-hoc subgroups

[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: BD, bronchodilator; CFB, change from baseline; CI, confidence interval; FEV1, forced expiratory volume in the first second; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error. The model with unstructured covariance structure was: CFB in FEV1 = treatment group + region + age + baseline FEV1 + visit + treatment * visit. Subjects with data at baseline and at least one post-baseline time point were included in the analysis. n1 = number of subjects contributing to the analysis (i.e. the number of subjects with at least one CFB value at any post baseline visit). n2 = number of subjects with a CFB value at each timepoint. Source: Adapted from Tables 50, 54, 58, 62 and 66, CS, Document B, Section B. 2.7.2.1.

Table 22: CFB to Week 48 in pre-BD FEV$_1$: SOURCE post-hoc subgroups

[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	

Abbreviations: BD, bronchodilator; CFB, change from baseline; CI, confidence interval; FEV$_1$, forced expiratory volume in the first second; LS, least squares; MMRM, mixed-effects model for repeated measures; mOCS, maintenance oral corticosteroid treatment; SE, standard error. Baseline is defined as the last non-missing measurement recorded on or prior to randomisation. Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + baseline FEV1 + visit + treatment * visit. Subjects with data at baseline and at least at one post-baseline time point included in analysis. Source: Adapted from Tables 70, 74, 78 and 82, CS, Document B, Section B.2.7.2.2.

Table 23: CFB in PEF and $FEF_{25–75\%}$ in NAVIGATOR and SOURCE

	NAVIGATOR (baseline-52 weeks)		**SOURCE (baseline-48 weeks)**	
	Tezepelumab	**Placebo**	**Tezepelumab**	**Placebo**
CFB in weekly morning PEF	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference in CFB in weekly morning PEF (95% CI; nominal p value)	[redacted]		[redacted]	
CFB in weekly evening PEF	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference in CFB in weekly evening PEF (95% CI; nominal p value)	[redacted]		[redacted]	
CFB in $FEF_{25–75\%}$	[redacted]	[redacted]	NA	
LS mean difference in CFB in $FEF_{25–75\%}$ (95% CI; nominal p value)	[redacted]		[redacted]	

Abbreviations: CFB, change from baseline; $FEF_{25–75\%}$, forced expiratory flow; PEF, peak expiratory flow; NA, not applicable; NR not reported

Health-related quality of life

AQLQ(S)+12 change from baseline data were reported in CS L.2.8, Table 56 and Figure 118 for PATHWAY, CS, Document B, Section B.2.6.2.4, Table 36 and Figure 15 for NAVIGATOR and CS, Document B, Section B.2.6.3.3 for SOURCE. In all three trials, AQLQ(S)+12 change from baseline was greater with tezepelumab 210 mg Q4W compared with placebo (see Table 24). The EAG note that this difference was not statistically significant at 52 weeks in PATHWAY. The Company also provide these data at Week 48 for PATHWAY (because of the large amount of missing data at 52 weeks), and a statistically significant between-group difference was reported (CS, Appendix L, Section L.2.8, Table 56, [redacted].

Table 24: AQLQ(S)+12 score CFB in PATHWAY, NAVIGATOR and SOURCE

	PATHWAY (baseline-52 weeks)		NAVIGATOR (baseline-52 weeks)		SOURCE (baseline-48 weeks)	
	[redacted]	[redacted]	Tezepelumab (n=528)	Placebo (n=531)	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	0.94	0.58
LS mean difference (95% CI)	[redacted]		[redacted]		0.36 (0.01, 0.70)	
p-value	[redacted]		[redacted]		NR	

Abbreviations: AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LS, least squares; NR, not reported. Source: Adapted from Table 36, CS, Document B, Section B.2.6.2.4; Table 56, CS L.2.8 and CS, Document B, Section B.2.6.3.3

AQLQ(S)+12 responder analyses were reported from PATHWAY (CS L.2.8, Table 57) and NAVIGATOR (CS, Document B, Section B.2.6.2.4, Table 37). Responders were defined as those who had a change from baseline AQLQ(S)+12 ≥0.5. In both studies, a greater proportion of subjects in the tezepelumab 210 mg Q4W arm were responders compared with those in the placebo arm at Week 52

[redacted]

EQ-5D-5L visual analogue scale (VAS) scores were also reported for all three key tezepelumab studies. For PATHWAY it was stated in CS L.2.10 that [redacted] However, no accompanying data were provided. For NAVIGATOR, CS, Document B, Section B.2.6.2.6 Table 41 reported [redacted] For SOURCE, CS, Document B, Section B.2.6.3.3 Table 47 reported that, over 48 weeks, and compared with placebo, those treated with tezepelumab had a greater improvement in EQ-5D-5L visual analogue scale scores (LS mean difference 7.21, 95% CI 1.01, 13.41, p<0.023). It was also stated that, in NAVIGATOR, tezepelumab improved scores and increased the [redacted] at 52 weeks compared with placebo, but accompanying data were not provided.

Adverse effects

On-treatment adverse events from PATHWAY, NAVIGATOR and SOURCE were reported in section B.2.10.1 and Tables 89 to 94 of the CS (CS, Document B, Section B.2.10.1 Tables 89 and 90 for PATHWAY, Tables 91 and 92 for NAVIGATOR and Tables 93 and 94 for SOURCE). A safety data pool combining PATHWAY and NAVIGATOR data, for tezepelumab 210 mg Q4W and for placebo, was provided in CS, Document B, Section B.2.10.3. The EAG agree that pooling these data is reasonable and also agree that data from SOURCE should additionally be considered. The EAG additionally agree that across the three trials, tezepelumab appears to be generally well-tolerated in patients with severe asthma.

AEs and SAEs

When compared with placebo arms, similar or lower proportions of participants in the tezepelumab 210 mg Q4W arms of the three key studies experienced at least one adverse event (AE) or serious adverse event (SAE). For AEs, these rates for telezpelumab and placebo respectively were 65.7% versus 65.9% in PATHWAY, [redacted] in NAVIGATOR, [redacted] in SOURCE and [redacted] in the pooled safety set. For SAEs, these rates for telezpelumab and placebo respectively were 9.5% versus 13% in PATHWAY, [redacted] in NAVIGATOR, [redacted] in SOURCE, and reported as [redacted] (although the EAG note that these figures [redacted] than for either PATHWAY of NAVIGATOR individually and that the reason for this is unclear).

The EAG highlight that data on AEs for the adolescent population (aged 12-17 years) were limited, based only on 82 participants in NAVIGATOR. CS, Document B, Section B.2.10.3.5, reported similar rates of AEs in adolescents for tezepelumab and placebo [redacted] respectively). The incidence of SAEs amongst adolescents was [redacted].

Treatment-related AEs and SAEs

Treatment-related AEs (TRAEs) were also found at similar rates for participants in the tezepelumab 210 mg Q4W and placebo arms of the three key studies. For PATHWAY, these data were reported as 10.2% versus 8.0% respectively, for SOURCE as [redacted] respectively, and for the pooled data [redacted]. B.2.10.1.2 of the CS states that, for NAVIGATOR, all AEs were deemed to be treatment-emeEargent unless otherwise stated, which would mean that TRAEs were [redacted] respectively for the tezepelumab 210 mg Q4W and placebo arms in this study. However, the EAG has checked the NAVIGATOR CSR and found that [redacted] The CSR data appear consistent with the data from the pooled safety data set where PATHWAY and NAVIGATOR safety data were combined.

In PATHWAY, only [redacted]. Again, for NAVIGATOR, because the CS states that all AEs were treatment emergent, [redacted]respectively of the tezepelumab and placebo arms would have experienced treatment-emergent SAEs. The EAG could not find any data on treatment-related SAEs in the NAVIGATOR CSR to clarify whether these data were accurately reported in the CS. However, it is unlikely that these data are accurate given that the data provided for the pooled safety set indicated that treatment-related SAEs across PATHWAY and NAVIGATOR were [redacted]

Discontinuations

In PATHWAY, two discontinuations (1.5%) occurred due to treatment with tezepelumab 210 mg Q4W (a single discontinuation occurred due to treatment with placebo), in NAVIGATOR 2.1% of participants in the tezepelumab arm discontinued due to treatment (3.6% discontinued due to placebo) and in SOURCE there were [redacted].

Deaths

Deaths were infrequent and where they [redacted]. There were no deaths reported in the tezepelumab 210 mg Q4W arm or placebo arm in PATHWAY. Two deaths were reported in NAVIGATOR; both were in the placebo arm, and [redacted]

Commonly reported AEs

The most frequently reported AEs in PATHWAY, occurring in at least 5% of participants, were asthma, nasopharyngitis, bronchitis, and headache (Table 25), with the latter three conditions occurring at similar frequencies in the tezeplemab 210 mg Q4W and placebo arms (asthma occurred at a greater frequency in the placebo arm). In NAVIGATOR, [redacted] were the most frequently reported AEs (Table 26), and with the exception of [redacted], these were reported at similar frequencies in the two study arms. In SOURCE, the most frequently reported adverse events were [redacted] in the tezepelumab arm and [redacted] (Table 27). [redacted] but there is also more uncertainty in this study due to the smaller sample sizes. The Company note that incidence of treatment-emergent anti-drug antibodies was low [redacted] and that [redacted]

Table 25: AEs reported in ≥5% of participants in PATHWAY (as-treated population)

Preferred term, n (%)[a]	Tezepelumab 210 mg Q4W (n=137)	Placebo (n=138)
Asthma[b]	27 (19.7)	50 (36.2)
Nasopharyngitis	19 (13.9)	16 (11.6)
Bronchitis	5 (3.6)	7 (5.1)
Headache	11 (8.0)	6 (4.3)

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; Q2W, once every 2 weeks; Q4W, once every 4 weeks. Notes: [a] Subjects were counted once for each preferred term regardless of the number of events; [b] The preferred term of asthma included all asthma events including protocol-defined asthma exacerbations. Source: Adapted from CS Table 90, B.2.10.1

Table 26: AEs reported in >3% of participants in NAVIGATOR (safety analysis set)

Preferred term, n (%)†	Tezepelumab (n=528)	Placebo (n=531)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Preferred term, n (%)†	Tezepelumab (n=528)	Placebo (n=531)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.

† Sorted by decreasing frequency for preferred term in subjects treated with tezepelumab.

Subjects with multiple events in the same preferred term were counted only once in that preferred term. Subjects with events in more than one preferred term were counted once in each of those preferred terms. Source: CS Table 92, B.2.10.1

Table 27: AEs reported in >3% of participants in SOURCE (safety analysis set)

Preferred term, n (%)†	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
† Sorted by decreasing frequency for preferred term in subjects treated with tezepelumab.
Subjects with multiple events in the same preferred term were counted only once in that preferred term. Subjects with events in more than one preferred term were counted once in each of those preferred terms. Source: CS Table 94, Section B.2.10.1

Amongst adolescents in NAVIGATOR, the most frequently reported AEs with tezepelumab and placebo were: [redacted]

AEs of special interest

Adverse events of special interest (AESIs) were reported for the safety pool in the text of the CS (CS, Document B, Section B.2.10.3.2). For clarity, the EAG has produced a summary table from the text provided by the Company (Table 28). The EAG agree that these data appear to be similar across study arms. The company state in The CS (Document B, Section B.2.10.3.2) that the data relating to [redacted].

[redacted] The company state in the CS (Document B, Section B.2.10.3.2, that across the three pivotal trials, there [redacted]. The EAG has confirmed this using the CSRs.

Table 28: AEs of special interest (pooled data from PATHWAY and NAVIGATOR)

AESIs n (%)	**Tezepelumab** **210 mg Q4W (n=665)**	**Placebo (n=669)**
Infections/infestations	13 (2.0)	15 (2.2)
Malignancies	6 (0.9)	5 (0.7)
Injection site reactions	25 (3.8)	21 (3.1)
Hypersensitivity [a]	56 (8.4)	58 (8.7)
SAE Hypersensitivity	1 (0.2)	2 (0.3)
Guillain-Barré syndrome	1 (0.2)	0 (0.0)

Key: AESIs, adverse events of special interest; SAE, serious adverse event; Q4W, once every 4 weeks. Notes:
[a] Narrow standard MedDRA query

Other clinical effectiveness data

The CS also reported data from NAVIGATOR on the following patient- and clinician-reported outcomes: St George's Respiratory Questionnaire (SGRQ), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C) and Clinician Global Impression of Change (CGI-C). Data on resource utilisation from NAVIGATOR and SOURCE were also reported. Table 10 provides the location within the CS of these data.

The EAG also note that pooled analyses (data from PATHWAY and NAVIGATOR) were provided in the CS for the following outcomes: AAER at 52 weeks, exacerbations associated with an ER visit/hospitalisation, change from baseline in FEV_1 over 52 weeks, change from baseline in AQLQ(S)+12 over 52 weeks and change from baseline in ACQ-6 over 52 weeks. Results from these pooled analyses can be found in CS Appendix D.5.1.2.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company identified a total of 36 trials to include in their network meta-analyses (NMAs). NMAs focused on five outcomes: AAER and AAER leading to hospitalisation, both measured using rates; change from baseline in ACQ score and in pre-BD FEV_1, both measured as mean differences; and change from baseline in OCS dose by reduction category (ordinal odds ratio). Only AAER, AAER leading to hospitalisation and change from baseline in OCS dose informed the economic model, and thus these are the focus below.

Appraisals of the trials were presented in CS Appendix D, section D.2.1.6, using item ratings without specific justification. It was not clear that risk of bias was imbalanced across different links in resulting evidence networks, with the exception that several omalizumab trials were not blinded.

The company undertook an assessment of heterogeneity in included trials. Key features relevant to assessing transitivity in NMAs related to differences in follow-up times, placebo equivalences, and most importantly, populations included in trials and the provenance of subgroups.

3.3.1. Differences in follow-up times

Across trials included in NMAs, differences in follow-up times may have affected the transitivity of networks of evidence; put otherwise, if trial-level average follow-up times are different across comparisons in networks, then indirect comparisons may be biased. The company discusses this issue in CS Appendix D, section D.2.1.4. In both AAER outcomes, trials with less than 52 weeks of follow-up compared omalizumab with placebo. It is unclear what the effect of this would be: if response is expected to improve over time, then it is possible that estimates of omalizumab comparative effectiveness may have been biased towards the null, but if loss of response is expected to be a significant factor, then a shorter follow-up could have benefited omalizumab. Weeks of follow-up for included studies were not provided for other outcomes where trials contributed to NMAs. In section D.2.1.4, the company notes evidence from clinical experts supporting the decision to pool different follow-up times; however, this did not appear to have been tested in sensitivity analyses or via meta-regression.

3.3.2. Placebo equivalences

Included networks often pooled different placebo ‘approaches’ under the same node, for example including best supportive care and optimised asthma therapy as part of placebo nodes. This was likely a reasonable assumption, as most patients in included trials were also on a background therapy. However, this was a target of sensitivity analysis.

3.3.3. Subgroup identification, provenance of subgroups and blending of subgroup evidence

As has been noted in Section 2, tezepelumab has a proposed positioning across a range of asthma indications defined by biomarkers and other characteristics (e.g. allergic asthma). This is a challenge to comparative effectiveness because included trials often enrolled a much wider population than the specific populations targeted for each drug type. In particular, and as noted by the company in Appendix D, trial populations varied by blood eosinophil (EOS) count, OCS use, baseline treatment, skin prick test, and IgE levels. These are often the categories used to define subgroups for analysis. A further potential issue in respect of specific populations is the treatment histories of patients in each trial. If patients in a given trial included in a specific network were previously on other drugs included in the network, then it is possible that NMAs in specific subgroups are considering patients for whom the trial drug is first, second or even third-line treatment. This is a possible threat to transitivity, albeit likely a minor one on balance.

For each outcome, the company estimated an ‘all-comers’ analysis, described as intention to treat (ITT). This analysis integrated evidence from whole populations in included trials. However, the company also undertook stratified NMAs focusing on specific clinically relevant subgroups. This is a strength, but it is also a drawback. A strength is that NMAs stratified by different categories can produce possibly less biased estimates of comparative effectiveness with respect to specific positions. A drawback is that the provenance of these subgroups—that is, where data were sourced from included trials—is unclear and could systematically differ over drugs in each network. Relatedly, networks for subgroups may not include all trials enrolling patients in that subgroup due to challenges in extracting subgroup data. This creates a potential source of selection bias in included NMAs, one that the company did not address directly by e.g. considering where trials that could have informed networks were not included.

In Appendix D Table 2, the company describes the subgroups for which data were sought. Below, in Table 29, the EAG summarises which of these subgroups were represented in NMAs. It is possible that not all NMAs undertaken were presented. For example, in clarification Table 5, the company refers to NMAs undertaken for AAER with respect to a subgroup of triple-positive patients. This result does not appear to have been presented in either the main body of CS Document B or in the appendices.

Finally, a key issue that arises is the need to blend evidence from different NMAs in the economic model. This is most notable to the extent that only an ITT NMA is available for the AAER leading to hospitalisation outcome, while stratified NMAs are available for the AAER outcome. This is important as populations in a subgroup NMA for AAER and in an ITT NMA for AAER leading to hospitalisation may be incommensurate, leading to biased inferences about the proportion of exacerbations leading to hospitalisation in each subgroup. This is addressed further in Section 4.2.6.

Table 29: Subgroups sought and presented in network meta-analyses

Subgroups of interest	AAER	AAER leading to hospitalisation	ΔACQ	ΔFEV	ΔOCS
ITT (all comers)	√	√	√	√	√
Patients with ≥3 exacerbations in the past year (severe)	√		√	√	
High EOS counts (eligible for IL-5 or IL-4 therapies)					
≥150 cells/µL	√		√	√	√ (also >50%)
≥300 cells/µL	√		√	√	√ (ZONDA, also >50%)
Low EOS counts					
EOS ≤150 cells/µL	√		√	√	
EOS ≤300 cells/µL	√		√	√	
High FeNO counts (eligible for IL-4 therapy)					
≥25 ppb	√			√	
≥50 ppb	√		√	√	
Patients with OCS-dependent asthma and EOS count more than 150 cells/ µL					
Patients with OCS-dependent asthma and EOS count less than 300 cells/ µL					
Patients with OCS-dependent asthma and EOS count more than 300 cells/ µL					
High EOS and FeNO counts (eligible for IL-4 therapy)					
≥150 cells/µL and FeNO ≥25 ppb					
≥150 cells/µL and FeNO ≥50 ppb					
≥300 cells/µL and FeNO ≥25 ppb					
≥300 cells/µL and FeNO ≥50 ppb					
Allergic asthma (i.e., high IgE) – eligible for anti-IgE therapy	√		√		
Triple-positive patients (high EOS, high FeNO, and high IgE counts)					

Subgroups of interest	AAER	AAER leading to hospitalisation	ΔACQ	ΔFEV	ΔOCS
EOS ≥150 cells/μL and FeNO ≥25 ppb with allergic asthma					
EOS ≥300 cells/μL and FeNO ≥25 ppb with allergic asthma					
EOS ≥150 cells/μL and FeNO ≥50 ppb with allergic asthma					
EOS ≥300 cells/μL and FeNO ≥50 ppb with allergic asthma					
Patients not eligible for any current biologic treatment					
Low EOS (<150 cells/μL) and FeNO (<25 ppb) counts					
Patients that switched from other biologic treatments					

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ, asthma control questionnaire; EOS, eosinophil; FeNO, Fractional Exhaled Nitric Oxide; FEV, forced expiratory volume; IgE, immunoglobulin E; ITT, intention to treat; OCS, oral corticosteroids

In CS document B, section B.3.3.2.2 describes how subgroup NMAs were mapped onto different populations for eventual use in the economic model. This approach was generally reasonable, with one caveat.

- For patients who were considered anti-IL5 eligible, subgroups considered were EOS count ≥300 cells/μL and ≥3 exacerbations in last 12 months; the company chose EOS count ≥300 cells/μL as the base case subgroup given the availability of subgroup NMA data for both AAER and change in OCS.
- For patients classed as dupilumab-eligible, the company noted that the preferred subgroup was EOS count <300 cells/μL given their assertion that 'in practice, for most patients (the adult population) this means the required EOS count is 150–299 cells/μL, so as not to be eligible for benralizumab and mepolizumab' (CS document B, p. 244). However, clinical advice to the EAG suggested that the EOS count ≥150 cells/μL would in fact be a more appropriate approximation so as not to include patients with EOS counts too low to be eligible. The EAG presents results from this NMA below.
- For patients classed as omalizumab-eligible, the company chose the AAER analysis for the subgroup of patients with allergic asthma. The EAG considered that this was appropriate.

Of note, the company comments that data on OCS reduction were only available from an ITT NMA for the duplilumab-eligible subgroup; but in fact, the OCS analysis was not relevant to this subgroup and did not enter into the model. For anti-IL5 eligible and duplilumab-eligible patient populations, the company also specified a range of subgroups as scenario analyses.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

Methods used for the NMAs were generally appropriate, drawing on random effects and fixed effects models with vague priors and Poisson, normal or probit links as appropriate to the outcome. In general, ITT NMAs drew on random effects models (with the exception of reduction in OCS dose, which only included four studies), while subgroup-specific NMAs drew on fixed effects models. NMAs were estimated in a Bayesian framework with three chains and ≥40,000 burn-in iterations, with ≥40,000 iterations from each chain preserved for analysis. While the company described an appropriate method for checking convergence, convergence diagnostics were not actually provided. At clarification, the company provided goodness of fit data comparing fixed effects and random effects models for each analysis specified (clarification

Table 5). This confirmed the company's general strategy with several exceptions possibly relevant to the economic model: deviance information criterion estimates for the AAER analysis for the EOS count ≥300 cells/µL and allergic subgroups suggested that a random effects model fit the data better than a fixed effects model. Because random effects estimates were not presented, it was not possible to verify why a fixed effects model would be preferable. Finally, the company did not state a method for testing and checking inconsistency in NMAs where this was necessary (i.e. where networks were star-shaped). The ERG was unable to follow this up comprehensively given time and resource constraints.

NMA results are presented for subgroups relevant to the economic model, and by outcome.

3.4.1. AAER estimates by subgroup

AAER NMAs for the ITT population were not used as part of a base case in the model and thus are not presented here.

3.4.1.1. High blood EOS level subgroup (≥300 cells/µL)

This fixed-effects NMA included 14 trials in an evidence network with one closed loop informed by three trials, of which one was multi-arm. Tezepelumab was numerically, but not statistically, better than all comparators with the exception of dupilumab at a non-recommended dose (see Table 30); however, tezepelumab was significantly better than placebo at reducing AAER compared to placebo ([redacted]).

Table 30. NMA results for AAER, EOS ≥300 cells/µL subgroup

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; CrI, credible interval; D, dupilumab; EOS, eosinophil; ITT, intent-to-treat; M, mepolizumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; O, omalizumab; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, reslizumab; T, tezepelumab.

Pairwise comparisons are shown in terms of rate ratios and 95% CrIs; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column; pink cells represent statistically significant differences between treatments.

Note: D 300 Q2W is not a NICE-recommended dose.

Source: CS document B, Figure 32.

3.4.1.2. Low blood EOS level subgroup (<300 cells/µL)

This fixed effects NMA drew on eight trials in an evidence network with one closed loop informed by three trials, of which one was multi-arm. Tezepelumab was numerically, but not statistically, better than all comparators in reducing AAER (see Table 31). An inconsistency test was not presented for this evidence network.

Table 31. NMA results for AAER, EOS <300 cells/µL subgroup

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; CrI, credible interval; D, dupilumab; EOS, eosinophil; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.

Pairwise comparisons are shown in terms of rate ratios and 95% CrIs; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column; pink cells represent statistically significant differences between treatments.

Note: D 300 Q2W is not a NICE-recommended dose.

Source: CS Document B, Figure 36.

3.4.1.3. High blood EOS level subgroup (≥150 cells/μL)

This fixed-effects NMA, which drew on a star-shaped network, drew on eight trials. Tezepelumab was numerically better than all comparators (see Table 32) and further statistically better than omalizumab (rate ratio [redacted], 95% CI [[redacted]]), benralizumab (rate ratio [redacted], 95% CI [[redacted]]) and placebo (rate ratio 0.38, 95% CI [[redacted]]).

Table 32. NMA results for AAER, EOS ≥150 cells/μL subgroup

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; O, omalizumab; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, reslizumab; T, tezepelumab.

Note: D 300 Q2W is not a NICE-recommended dose.

Source: CS document B, figure 30

3.4.1.4. Allergic asthma subgroup

This fixed-effects NMA, which drew on a star-shaped network, included 11 trials. Findings (see Table 33) demonstrated that in the allergic asthma subgroup, tezepelumab was numerically better than all comparators in reducing AAER; though this difference was only statistically significant for comparisons against placebo, with a modelled [redacted] reduction in AAER (95% CI [redacted]).

Table 33: NMA results for AAER, allergic asthma subgroup

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; CrI, credible interval; D, dupilumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; O, omalizumab; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, reslizumab; T, tezepelumab.

Pairwise comparisons are shown in terms of rate ratios and 95% CrIs; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column; pink cells represent statistically significant differences between treatments.

Note: D 300 Q2W is not a NICE-recommended dose.

Source: CS document B, figure 44.

3.4.2. AAER leading to hospitalisation estimates

The only NMA available for this outcome was in the ITT population. This random-effects NMA drew on 11 trials in a star-shaped network. Tezepelumab was numerically but not significantly better than all comparators in reducing AAER leading to hospitalisations (see Table 34) but was only significantly better than placebo ([redacted]).

Table 34. NMA results for AAER leading to hospitalisation, ITT

[redacted]

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; CrI, credible interval; D, dupilumab; ITT, intent-to-treat; M, mepolizumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; O, omalizumab; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; R, reslizumab; T, tezepelumab.

Pairwise comparisons are shown in terms of rate ratios and 95% CrIs; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column; pink cells represent statistically significant differences between treatments.

Note: D 300 Q2W is not a NICE-recommended dose.

Source CS document B, figure 46

3.4.3. OCS reduction estimates

Only the OCS reduction estimates for EOS ≥300 cells/µL subgroup are presented here, including all eligible trials (three trials). This star-shaped network did not find any relative differences between comparators, though tezepelumab performed best numerically (see Table 35). However, this was not the case in an ITT NMA for this outcome, where tezepelumab performed second to last, was not significantly different from placebo and was significantly worse than benralizumab and dupilumab (CS document B, figure 48).

Table 35. NMA results for OCS reduction, EOS ≥300 cells/μL subgroup

[redacted]

Abbreviations: B, benralizumab; CrI, credible interval; EOS, eosinophil; M, mepolizumab; NMA, network meta-analysis; OCS, oral corticosteroid; PBO, placebo; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.

Pairwise comparisons are shown in terms of rate ratios and 95% CrIs; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column; pink cells represent statistically significant differences between treatments.

Source: CS document B, figure 54.

3.4.4. Sensitivity analyses

The company presented a range of sensitivity analyses, including only blinded studies, including only phase III or IV studies, and using baseline risk adjustment. Given the sparsity of the OCS reduction NMA, sensitivity analyses were not reported for this outcome. No sensitivity analyses changed the qualitative conclusions of NMAs.

3.4.5. Simulated treatment comparisons

The company also presented in Appendix D a set of simulated treatment comparisons (STCs) drawing on data from NAVIGATOR and SOURCE. However, these STCs were not used in the economic model, and the EAG does not summarise their results here in depth. In short, STCs could only one trial (or pooled analysis) could be included in any one STC. By corollary to this, tezepelumab could only be compared against one other drug in any analysis, meaning that for the anti-IL5 eligible class, each pairwise comparison with tezepelumab was presented separately. Nearly all resultant comparisons were thus highly imprecise in their estimation. While it is an advantage of STCs that multiple effect modifiers can be included in the analysis to ensure balance, this also requires the availability of all effect modifiers for inclusion.

3.5. Additional work on clinical effectiveness undertaken by the EAG

No additional work on clinical effectiveness was undertaken by the EAG.

3.6. Conclusions of the clinical effectiveness section

The EAG considered that the company's SLR was reasonably likely to have identified the relevant evidence related to tezepelumab and key comparators and that the methods of the SLR and those of the key tezepelumab studies (PATHWAY, NAVIGATOR and SOURCE) were reasonably well described.

The key tezepelumab trials (PATHWAY, NAVIGATOR and SOURCE) were generally relevant to the company's decision problem and covered the relevant outcomes in the NICE final scope (contrary to the company's decision problem and economic modelling, reslizumab was included as a comparator in the SLR and resulting NMAs). However, all three trials allowed the inclusion of participants using at least medium dose ICS, which risks the inclusion of under-treated participants who may be more likely to experience exacerbations. Conversely, PATHWAY and NAVIGATOR both allowed the inclusion of participants with at least two (rather than three) exacerbations, with PATHWAY additionally including participants who had experienced any severe exacerbation resulting in hospitalisation in the preceding 12 months. These participants may benefit less from treatment than those specified in the decision problem. Overall, the results of PATHWAY, NAVIGATOR and SOURCE were reasonably well described in the CS, but the EAG note that some subgroup analyses for secondary outcomes were not reported.

In order to compare tezepelumab against other active agents (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) the company relies on NMAs. Methods used for the NMAs were generally appropriate, drawing on random effects and fixed effects models with vague priors and Poisson, normal or probit links as appropriate to the outcome.

However, transitivity in NMAs was likely impacted by differences in follow-up times, and to a lesser extent, placebo equivalences. With regards to differences in follow-up times, the trials comparing omalizumab with placebo included follow-up of less than 52 weeks for both AAER outcomes; it is unclear in which direction this might bias results. The Company notes evidence from clinical experts supporting the decision to pool different follow-up times, but this did not appear to have been tested in sensitivity analyses or via meta-regression. The EAG note the issue of placebo equivalences (including different comparator 'approaches' under the same nodes), but note that because most participants were also on background therapy, this was not an entirely unreasonable approach.

More importantly, the EAG highlight a key issue likely impacting upon NMA transitivity: the provenance of subgroups. Subgroups were generally defined by biomarkers but data were not consistently available for all relevant trials. No subgroup data were available for the NMA of AAER leading to hospitalisations. This means that model inputs draw on NMAs from a blend of populations, and the provenance of subgroups from included trials is unclear. The EAG has used alternative assumptions for the split of hospitalised exacerbations, as the blending of NMA populations generated results that lacked credibility.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

Appendices G, H and I of the CS detail systematic searches of the literature used to identify cost effectiveness, health-related quality of life, healthcare resource use and costs evidence, critique is provided in Table 36, Table 37, and Table 38. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

Table 36. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G, Section G.1	The searches of bibliographic databases and sources are considered broadly appropriate, however, the filter used in MEDLINE and Embase to identify cost-effectiveness studies is not recognised by the EAG as a validated filter.
Inclusion criteria	Appendix G, Section G.2	The inclusion criteria are broad and therefore likely to have captured the available evidence. The EAG noted that 14 abstracts were included in the review but data extraction was not completed. The company responded to provide citations for the 14 abstracts and clarified that due to limited reporting of key aspects of model methodology/structure and outcome data in publications, it limited studies for detailed extraction to those reported as full publications. The EAG noted that of the 14 abstracts, there was one UK-based abstract (Faria 2013) but as this is reported in full in the included Faria 2014 this was not considered to be an issue.
Screening	Appendix G, Section G.2.1	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	Appendix G, Section G.2.1	Data extraction was completed by one reviewer with a second reviewer checking the extraction and disagreements resolved through discussion
QA of included studies	Not reported	The methodological quality of included full text publications was not assessed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 37. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix H, Section H.1	The searches of bibliographic databases and sources are considered broadly appropriate, however, the filter used in MEDLINE to identify health-related quality of life studies is not recognised by the EAG as a validated filter. The filter applied does not include relevant controlled vocabulary (for e.g. Quality-Adjusted Life Years/). The EAG is satisfied that company searches of multiple bibliographic databases and other sources are likely to have mitigated this issue and identified all relevant literature.
Inclusion criteria	Appendix H, Section H.2	The inclusion criteria are broad and therefore likely to have captured the available evidence.
Screening	Appendix H, Section H.2.1	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	Appendix H, Section H.2.1	Data extraction was completed by one reviewer with a second reviewer checking the extraction and disagreements resolved through discussion
QA of included studies	Not reported	The methodological quality of included full text publications was not assessed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 38. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix I.1	The searches of bibliographic databases and other sources are considered broadly appropriate.
Inclusion criteria	Appendix I, Section I.1	The inclusion criteria are broad and therefore likely to have captured the available evidence.
Screening	Appendix I, Section I.2	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.

Systematic review step	**Section of CS in which methods are reported**	**EAG assessment of robustness of methods**
Data extraction	Appendix I, Section I.2.1	Data extraction was completed by one reviewer with a second reviewer checking the extraction and disagreements resolved through discussion
QA of included studies	Appendix I, Section I.2.1	The methodological quality of included full text publications was not assessed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 39: NICE reference case checklist

Attribute	**Reference case**	**EAG comment on company's submission**
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS does not explicitly state whose health outcomes are included, but the EAG infers that the outcomes relate to patients with severe asthma (i.e. carer outcomes are not included). This is consistent with the NICE reference case.
Perspective on costs	NHS and PSS	The CS does not explicitly state the cost perspective but included resource use items are consistent with the NICE reference case (NHS and PSS).
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	As per reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model has a time horizon of 60 years. Given the need for lifetime treatment this is appropriate.
Synthesis of evidence on health effects	Based on systematic review	Transition probabilities for patients treated with tezepelumab and SoC were based on patient level data observed in the NAVIGATOR[2] and SOURCE[3] studies. Relative exacerbation rates of other comparator treatments were based on a network meta-

Attribute	Reference case	EAG comment on company's submission
		analysis. This is broadly appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As per reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	As per reference case (extracted from NAVIGATOR[2] and SOURCE[3] trials).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	van Hout cross-walk algorithm for EQ5D5L[36] (stated in NAVIGATOR[2]). Consistent with reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use items and unit costs appear consistent with the NICE reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per reference case.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The model is a Markov model divided into five health states: controlled asthma, uncontrolled asthma, uncontrolled asthma with exacerbation, controlled asthma with exacerbation and dead (CS Document B, section B3.2.2). Furthermore, health states are divided into whether or not the patient is taking mOCS. Thus there are effectively nine discrete health states. Controlled asthma is defined as ACQ <1.5 and uncontrolled as ACQ ≥1.5. An exacerbation is defined as a worsening of the patient's asthma requiring either a burst of OCS for at least three consecutive days, an ED attendance or hospitalisation. The transition period is four weeks.

The EAG considers a Markov model to be an appropriate structure to model treatments for asthma. However, the EAG questions the company's approach to modelling exacerbations as 'controlled' and 'uncontrolled' exacerbations. This is discussed in more detail in Section 4.2.6.3.

4.2.3. Population

The company used baseline characteristics (age, gender, % mOCS and baseline dose of mOCS) from a large UK prospective cohort study.[32] This is likely to improve the relevance of the analysis to the UK setting, compared with using baseline characteristics observed in the pivotal trials.

4.2.4. Interventions and comparators

The company excluded reslizumab as a comparator on the grounds that it does not represent current practice in England: a recent (2021) analysis of the UK Severe Asthma Registry observed that 9/2,225 severe asthma patients received reslizumab (0.4%, or 0.6% of those treated with a biologic, see Table 5).[32] Whilst the NICE methods guide (2013) does state that established NHS practice is a basis for judging appropriateness of including a comparator, it also states that existing NICE guidance, cost-effectiveness and licensing status of the comparator are also valid criteria. Reslizumab received a positive recommendation from NICE in October 2017.[26]

The EAG considers exclusion on the grounds of current practice a weak justification: a comparator may not represent current practice simply due to lack of promotion/marketing by the manufacturer or novelty of the drug. This does not mean it *should* not be used or considered in routine practice. The EAG notes that reslizumab is an IV drug whereas others are oral. However, a scenario where oral therapies are much more expensive than IV may lead to situations where it is more efficient to recommend the IV therapies as this releases resources to better effect to other patients, rather than consuming all the resources on the oral therapies. Inclusion of the IV therapy in the decision model allows this to be confirmed or refuted.

The EAG further notes that according to the same data source, dupilumab was used in an even smaller proportion of patients (n=5, 0.3%), but the company considered this an appropriate comparator in one of the subgroups. It has therefore been inconsistent in its justification to selection of comparators. The EAG considers the fact that reslizumab has a positive recommendation from NICE a much stronger criterion than usage statistics and therefore it should be included as a comparator. Please note that the EAG's analyses includes reslizumab as a comparator and the results for the reslizumab eligible population have been presented in Section 6.2.10 and Section 6.3.

4.2.5. Perspective, time horizon and discounting

These are all in line with NICE guidance. The time horizon was 60 years, which the EAG considers appropriate.

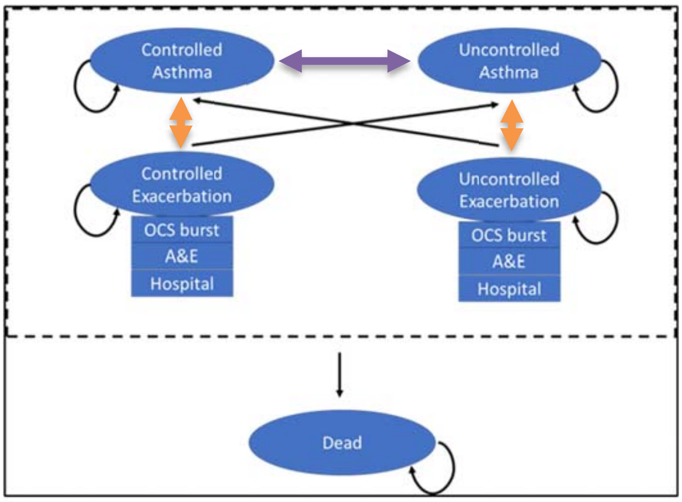
4.2.6. Treatment effectiveness and extrapolation

The company states (CS, Document B, Section B.3.3.2) that the model captures treatment effectiveness through:

1. Reduction in rate of exacerbations
2. Reduction in severity of exacerbations that do occur (specifically reduced probability of hospitalisation).
3. Reduction in ACQ-6 score
4. OCS sparing

Point 1 is enacted through transition probabilities for movement between 'controlled' or 'uncontrolled' health states and their respective 'exacerbation' health state (Figure 10, orange arrows). Point 2 is enacted by changing proportions of OCS burst vs ED attendance vs hospital admission when an exacerbation does occur. Point 3 is enacted through transition probabilities between the 'controlled' (ACQ <1.5) and 'uncontrolled' (ACQ ≥1.5) asthma health states (Figure 10, purple arrows), and Point 4 is enacted through changes in transition probabilities (a different set is attributed to patients taking mOCS vs those without) and reduced probabilities of long-term consequences of OCS.

Figure 10: Model Structure



Adapted from Figure 62, CS, Document B, Section B.3.2.2, P219

Furthermore, the company makes changes to the transition probabilities at Week 52 (representing 'post response assessment'). The justification for this is to account for non-response and subsequent discontinuations at a 52-week response assessment.

Transition probabilities for tezepelumab and SoC were calculated based on patient counts every four weeks in each health state from the NAVIGATOR and SOURCE studies. The precise method by which the two sources were combined is not stated explicitly but the EAG infers that probabilities for patients without mOCS were estimated from NAVIGATOR and for those taking mOCS from SOURCE. This unadjusted approach is only valid if the trial populations and treatment regimens within NAVIGATOR and SOURCE are identical. A meta-analytic approach may have been preferable, but in the view of the EAG, given the similarities of the study designs, any bias is likely to be small. Transition probabilities for other treatments were based on a network meta-analysis estimating rate ratios (see Section 3.4 of this report).

The EAG notes a number of issues with the company's approach:

- Using an ACQ cutoff of <1.5 will classify patients with partially controlled asthma as fully controlled.
- Transition probabilities post response assessment may overestimate treatment effectiveness.
- The model differentiates between a 'controlled' and 'uncontrolled' exacerbation, restricting some transitions (eg controlled asthma to an 'uncontrolled exacerbation').
- Hospitalisation rates from exacerbations are likely overestimated for biologic therapies other than tezepelumab.

These are considered in turn below.

4.2.6.1. ACQ cut-off

The EAG notes that the ACQ score of 1.5 is consistent with the authors of the ACQ's definition of "…[being]… confident that a patient has *inadequately* controlled asthma… (positive predictive value = 0.88)" (emphasis added).[4] Juniper et al. (ibid) also state "..the analysis showed that the crossover point between 'well-controlled' and 'not well-controlled' is close to 1.00 on the ACQ. To be confident that a patient has *well-controlled* asthma, the optimal cut-point is 0.75 (negative predictive value = 0.85)" (emphasis added). The NAVIGATOR clinical study report also defines an ACQ between 0.75 and <1.5 as ‘partially controlled’ (NAVIGATOR CSR Section 9.7.3.2, P85).[2]

Therefore, the company’s model classifies patients with partial control as full control, thus overestimating the effectiveness of treatments. A cut-off of 1.00 on the ACQ would have been more appropriate. The EAG was not able to recalculate the transition probabilities with the data presented. However, a scenario analysis partially approximating this by multiplying relevant transition probabilities by the PPV (0.88) was explored. See Section 6.2.7.3 for further details.

4.2.6.2. Transition probabilities post-assessment

The company model uses a different set of transition probabilities post 52 weeks, the driver of which is a surge in discontinuations following assessment at one year. However, the CS states:

“As no data were available for patients beyond the assessment point of 52 weeks from the trial, efficacy for responders was informed using the subgroup of patients who were deemed responders across the first 52 weeks as an assumption.” (CS, Document B, Section B.3.3.2.1, p228).

“As no clinically meaningful definition to define response was available from the tezepelumab pivotal trials, the model assumed that the definition of response was any reduction in the rate of exacerbation or mOCS dose from baseline.” (CS, Document B, Section B.3.2.2.3, p220).

This leads to a small reduction in the risk of exacerbation in the tezepelumab arm (and via the relative risks from the NMA, other biologic treatments), and in particular an improved chance of recovery from exacerbation (CS, Document B, Tables 101-104). In summary, the model effectively assumes that the effectiveness of tezepelumab and other biologics increases, due to there being fewer non-responders in the pool of patients who continue to take the drug (who transition to SoC). Whilst this is plausible, the EAG is of this opinion that this is likely an overestimate as the model incorporates background discontinuation already. Thus, the transition probabilities prior to Year 1 should already reflect discontinuations. It would have been preferable for the company to model transition probabilities as a function of time, rather than a step function at Week 52.

Furthermore, the post-assessment transition probabilities are based on company’s definition of response as per the quote above. As mentioned in Table 6 (outcomes), the clinical opinion to EAG indicated that any reduction in exacerbation is not necessarily clinically meaningful, however, a reduction of 20-50% is worthwhile to be considered as a response. Therefore, under a different definition of response, for example a 20% reduction in exacerbations, the post-assessment transition probabilities are likely to change. This adds to the uncertainty associated with the post-assessment transition probabilities applied after 52 weeks. To explore this uncertainty EAG has considered a scenario where post-assessment transition probabilities are assumed to be the same as pre-assessment transition probabilities. See section 6.2.7.1 for further details.

4.2.6.3. Differentiation between Controlled and Uncontrolled Exacerbations and respective transition probabilities

The model defines two types of exacerbation, 'controlled' and 'uncontrolled'. Conceptually, a patient experiencing an exacerbation is by definition in an uncontrolled state at that time point, and the ACQ score would be expected to be highly positively correlated with this: ACQ questions include self-rated symptom severity on waking, frequency of shortness of breath and wheezing. The EAG agrees with the company that it may be useful within the model to differentiate the previous control status, on the grounds that a patient with well controlled asthma is more likely to return to a well controlled state following an exacerbation (and likewise for patients with poorly controlled asthma). However, the EAG is concerned that as designed, the model actively prohibits some transitions, specifically from controlled asthma to uncontrolled exacerbation (and uncontrolled asthma to controlled exacerbation, as per Figure 10):

"Patients could not transfer from controlled asthma to uncontrolled exacerbation. If this were the case, i.e. a drop in ACQ score simultaneously with an exacerbation, the patient would have entered controlled exacerbation (i.e. any change in ACQ score was assumed to be due to the exacerbation itself where an exacerbation was ongoing)" (CS, Document B, Table 138, P267)

Further, it seems likely that the transition probabilities from exacerbations to controlled asthma health state are overestimated. This is because patients transitioning from the controlled exacerbation state are more likely to return to the controlled state rather than uncontrolled. However, clinical expert opinion to EAG indicated that: "*Baseline stage is either controlled or uncontrolled. In either of those states, patients can exacerbate, but there would be a different risk of exacerbation so your transition probability will be different depending on where you start and after the exacerbation, where patients would go back to probably is dependent on where they came from. If patients were uncontrolled and exacerbating, they are perhaps more likely to* *go back to being uncontrolled than to being controlled. Whereas if they were controlled and exacerbate they could go back to either being controlled again or to being uncontrolled*."

Though the company model considers transition from controlled exacerbation state to uncontrolled asthma state, those probabilities are lower than that of the transitions from controlled exacerbation state to controlled asthma state in many instances. For example, in Table 40 (from CS, Document B, Table 101) provided below for anti-IL5 eligible group, the probability of transitioning (both pre- and post- assessment) into the controlled asthma state from controlled exacerbation state is >50%, which might underestimate the patients moving to uncontrolled asthma following a controlled exacerbation.

Table 40: Transition probabilities (Anti-IL-5 eligible)

Tezepelumab: Pre-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]
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]

Abbreviations: CS, company submission; IL-5 , interleukin-5; OCS, oral corticosteroids; 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.

Source: CS, Document B Table 101

Due to the manner in which the model was coded, the EAG was unable to either restructure the model with a single 'exacerbation' health state, or modify all relevant transition probabilities. The EAG has therefore explored an analysis where the utilities for controlled and uncontrolled exacerbations were assumed to be equal (please note that costs are already equal between the two in the company's model) as presented in Section 6.2.1 and where the transition probabilities for moving out of controlled exacerbations are the same as that of uncontrolled exacerbations (Section 6.2.7.2).

4.2.6.4. Hospitalisation rate for biologics other than tezepelumab may be overestimated

The model implements hospitalisation rates in a manner that may overestimate hospitalisations in biologic therapies other than tezepelumab.

The rate of exacerbations and hospitalisations in the tezepelumab and SoC arms are drawn from observed count data from the NAVIGATOR and PATHWAY studies. These and count data from other studies comparing other biologics are combined in a network meta-analysis, with results reported as rate ratios (all relative to placebo, assumed to represent SoC). The decision model draws on NAVIGATOR and SOURCE to estimate the probability of an exacerbation, then applies the rate ratios (with appropriate transformation between rates and probabilities) to calculate the probability of an exacerbation with the various other biologic therapies.

The probability of exacerbation leading to hospitalisation for tezepelumab and SoC was appropriately calculated directly from NAVIGATOR and SOURCE by dividing the number of hospitalisations by the number of exacerbations. However, to calculate the proportions for other biologics, the company appears to have multiplied the proportion in the tezepelumab arm by the rate ratio based on total rate of exacerbations leading to hospitalisations from the NMA, rather than the *proportion* of exacerbations leading to hospitalisation. If so, this is incorrect and can substantially overestimate the hospitalisation rates amongst other biologic therapies.

For example, suppose patients on Drug A had a mean of two exacerbations per patient per year, one of which required hospitalisation. Patients taking Drug B experienced four exacerbations, two of which led to hospitalisation. In both cases, the proportion requiring hospitalisation is 50% (Table 41). The company's approach correctly uses the rate ratio of 2 to calculate exacerbations for Drug B (Row 1, Table 41), but appears to incorrectly use the rate ratio for all hospitalisations (of 2) to calculate the proportion requiring hospitalisation (Row 2 of Table 41) rather than the relative risk of 1 (Row 3 of Table 41).

Table 41: Exacerbations and Hospitalisations example

Row		Drug A	Drug B	RR
1	Exacerbations	2	4	2

Row		Drug A	Drug B	RR
2	Hospitalisations	1	2	2
3	Proportion of exacerbations leading to hospitalisation	0.5	0.5	1

Abbreviations: RR, relative risk

Note: Exacerbations and hospitalisations are per patient per year. RR: rate ratio (exacerbations and hospitalisations) or relative risk (% of exacerbations leading to hospitalisation).

Furthermore, the EAG notes a recent network meta-analysis of monoclonal antibodies in type 2 asthma by Edris et al. (2019).[37] This demonstrated that none of the biologics showed statistically significant improvement in the exacerbation rate (as well as the exacerbations leading to hospitalisation rate) compared to the pooled placebo, neither was any superiority identified in the indirect head to head comparisons amongst the treatments.

The EAG explored an alternative scenario assuming the same probability of hospitalisation for exacerbations for all biologic therapies. See Section 6.2.4 for further details.

4.2.7. Health-related quality of life

The company's model includes a utility increment of [redacted] for patients treated with a biologic therapy, over and above any impact on asthma control or risk of exacerbations. The EAG notes this is of borderline statistical significance in the company's regression model (p=0.049) and feels that there is no logical justification for this: it is likely a chance finding.

The EAG raised this as a query with the company at clarification stage. The company's response stated that there were (1) elements of HRQoL not captured by ACQ or exacerbations and (2) elements of ACQ that are not captured within the model structure.

With respect to (1), the company claims that the ACQ-6 excludes FEV1 measurement (which is included in the ACQ-7), and airway hyperresponsiveness. However, these are clinical measures. The purpose of quality-of-life measurement is to translate the impact of clinical measures on to dimensions of quality of life and thus further inclusion would be double counting. Furthermore, the authors of the ACQ explored the measurement properties of various shortened versions of the original 7-item ACQ, concluding "*the results and interpretation of clinical studies will not be affected if the questions concerning airway calibre and rescue bronchodilator use are omitted from the ACQ*".[38]

With respect to (2), the company argues that dichotomising patients' asthma into 'controlled' and 'uncontrolled' loses information and that within controlled and uncontrolled health states, ACQ per person was consistently lower in patients treated with tezepelumab compared with placebo (Figure **11** and Figure **12** below). However, the EAG notes that the differences are approximately [redacted] to [redacted] points in the controlled state and between [redacted] and [redacted] in the uncontrolled state. These are well within the clinically meaningful difference of 0.5 points,[38] and therefore any difference in quality of life is likely to be either zero or very close to.

Figure 11: Controlled health state, ACQ score Tezepelumab vs Placebo

[redacted]

Definition: Controlled ACQ-6 at each visit includes subjects with well controlled (ACQ-6 score ≤0.75) or partially controlled ACQ-6 (0.75 <ACQ-6 score <1.5). Abbreviation: ACQ, Asthma Control Questionnaire.

Figure 12: Uncontrolled health state, ACQ score Tezepelumab vs Placebo

[redacted]

Definition: Uncontrolled ACQ-6 at each visit includes subjects with ACQ-6 score ≥1.5. Abbreviation: ACQ, Asthma Control Questionnaire.
Reproduced from company clarification response to Clarification Question B10

The EAG conducted a scenario excluding the biological treatment utility gain (i.e., setting the co-efficient on biological treatment to zero) as detailed further in Section 6.2.3.

4.2.8. Asthma mortality

The company's model assumes death from asthma can only occur through an exacerbation over and above background mortality rates. Death rates following hospitalisations were estimated from a study drawing on UK data between 2000-05,[39] and a study drawing on Scottish data from 1981-2009.[40] Death rates following OCS burst or A&E attendance were estimated from the 2014 National Review of Asthma Deaths (NRAD) report.[41]

The EAG is concerned that the probabilities used by the company overestimate asthma-related mortality for the population aged <75 years. As noted in the Health Survey for England (HSE) asthma report 2018: "*Almost three-quarters of asthma deaths occur in people aged 75 and over and only one-quarter occur in adults aged 35 to 74 years*". However, the asthma mortality for adults aged <75 years has been overestimated in the company's model; for example, in the SoC arm, ~37% of deaths occur in the cohort <75 years which is roughly 12% more than the HSE (2018)[42] asthma report estimate as mentioned above.

Issues with mortality validation have occurred in other asthma appraisals. In NICE TA565 for benralizumab, the EAG indicated that the asthma death estimates used in the company's model were ~2.5 times higher than the estimates based on the British Thoracic Society adult asthma audit report (2016);[43] this source was later preferred by the committee for people aged 45-64 years.[23] However, in this appraisal, the EAG performed an ad hoc search for the latest asthma mortality data and located the 2020 asthma mortality data and the number of admission episodes for England (cause of death: J45-J46 Asthma) from the Office of National Statistics (ONS; nomis database).[44]

Based on the 2020 asthma mortality data which indicated 1,259 asthma deaths out of 83,659 admissions, the average probability of death (annual probability converted to four-weekly) was 0.00116575. The average probability of death (four-weekly) in hospital setting based on company's asthma mortality estimates used in the model for people aged <65 years was 0.006778, about five times higher than the 2020 asthma mortality data derived from ONS. It is to be noted that overestimating mortality leads to overestimating the potential gain from prevention of exacerbations, and thus will overestimate the effectiveness of tezepelumab.

Therefore, the EAG adjusted the per cycle probabilities of asthma deaths for adults <75 years by a factor of 0.2. The company's probabilities and the EAG estimated probabilities of death are presented below (Table 42).

Table 42. Asthma mortality estimates (exacerbation related)

	Company's model		**EAG model**
Age band (years)	**Probability of death (4-weekly)**	**Source: Watson et al. 2007, Roberts et al. 2013, NRAD 2014**	**Probability of death (4-weekly)**
OCS burst			
18-44	0.000481	Watson et al. + NRAD	0.0000962*
45+ ^	0.003115		0.0006230*
ED visit			
18-44	0.004930	Watson et al. + NRAD	0.0009860*
45+ ^	0.031894		0.0063788*
Hospitalisation			
18-24	0.001456	Roberts et al.	0.0002912*
25-34	0.001443		0.0002886*
36-44	0.002011		0.0004022*
45-54	0.007560	Watson et al. fitted to Roberts et al.	0.0015120*
55-64	0.021420		0.0042840*
65+	0.045360		Same as CS

Abbreviations: CS, company submission; EAG, External Assessment Group; ED, emergency department; NRAD, National Review of Asthma Deaths; OCS, oral corticosteroids

* derived by multiplying the company's probability by 0.2

^ as the risk is the same for people aged 45+ years in case of exacerbations leading to OCS burst and ED visit, EAG's adjustment of probability (company's probability multiplied by 0.2) was applied here as well

As can be seen from the table below (Table 43), with the EAG derived mortality estimates the percentage of deaths in the 49-74 age group is closer to that of the HSE asthma report (2018).

Table 43. Model predicted deaths: Company vs EAG model (SoC)

Age band	**Model prediction based on company's estimates**		**Model prediction based on EAG estimates**	
	Deaths (n)	**%**	**Deaths (n)**	**%**
49-74	360	37%	262	27%
75-100	625	63%	718	73%
49-100	*985*	*100%*	*980*	*100%*

Abbreviations: EAG, External Assessment Group; SoC, Standard of care

Further, the model predicted life expectancy of the populations considered have been provided in the table below (Table 44), using both company used and EAG derived asthma mortality estimates. It is evident that that the life expectancy is slightly higher in all subgroups with the EAG derived estimates (though still lower than the UK life expectancy for the respective subgroups).

Table 44. Model prediction of life expectancy (years)

	Based on asthma mortality probabilities		UK life expectancy for ~50-year-old person*
	Company used	EAG derived	
Dupilumab-eligible			
Tezepelumab	77.95	83.19	85.87
Dupilumab	77.17	82.88	
Anti IL5-eligible			
Tezepelumab	78.39	81.32	85.83
Benralizumab	78.11	81.27	
Mepolizumab	78.13	81.23	
Reslizumab-eligible			
Tezepelumab	78.79	81.52	
Reslizumab	78.64	81.50	
Omalizumab-eligible			
Tezepelumab	77.30	81.51	86.01
Omalizumab	76.64	81.31	
Non-bio eligible, 3+ exacerbations or mOCS			
Tezepelumab	79.85	81.85	85.87
SoC	78.28	81.35	

* based on proportion male (as per Jackson et al 2020) for the respective subgroups

4.2.9. Resources and costs

Resource use items included drug acquisition cost, disease management costs (primary care contacts and outpatient respiratory specialist consultations), OCS-related adverse event costs (representing long term complications such as T2DM, osteoporosis, and ocular, cardiovascular, renal, gastric and pulmonary diseases). Drug acquisition costs were calculated per four-week cycle, taking into account higher dosing in Year 1 where appropriate (CS, Document B, Section B.3.5.1, Table 134, p262). Disease management costs comprised routine primary and secondary contacts and were extracted from a previous study (Willson 2014).[45] Contact frequencies varied by asthma state (controlled vs uncontrolled) and exacerbation with or without hospitalisation.

The source study for contact frequencies (Willson 2014)[45] is a decision model-based analysis of tiotropium in patients with poorly controlled asthma, with an RCT as the major input. Willson et al. abandoned use of their own resource use data from the RCT to inform the model due to lack of clarity between protocol-driven and medically necessary contacts, instead conducting a survey of 15 UK health care providers (five GPs, five asthma specialists and five asthma nurses) to estimate routine health care contacts. The CS used the results of this survey to inform routine disease management costs. Willson et al.[45] reported standard deviations around resource use quantities, but owing to the way the questionnaire was phrased and lack of reporting clarity regarding merging the opinions of the 15 experts (eg the approach appears not to have taken into account epistemic uncertainty), it is not possible to verify or calculate standard errors. The company assigned as an arbitrary estimate one tenth of the mean as a standard error, which given the data limitations, appears reasonable, although in the subjective opinion of the EAG, may underestimate uncertainty.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The results reported by the company are shown in Table 45 - Table 48. The deterministic and probabilistic results suggest tezepelumab dominates other treatment options in three of the four subpopulations and yields an incremental cost-effectiveness ratio (ICER) of £[redacted] (deterministic) or £[redacted] (probabilistic) per QALY gained versus SoC in the non-biological eligible subpopulation. Note the CS presents pairwise rather than fully incremental differences in cost and QALYs. The EAG has corrected increments for benralizumab accounting for this.

Table 45: Company base case results (anti-IL-5 eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Company probabilistic base case					
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: QALYs, quality adjusted life years; SoC Standard of Care

Table 46: Company base case results (dupilumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

	Discounted costs	**Discounted QALYs**	**Incremental discounted costs**	**Incremental discounted QALYs**	**Cost per QALY gained**
Company probabilistic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; SoC, standard of care

Table 47: Company base case results (omalizumab eligible)

	Discounted costs	**Discounted QALYs**	**Incremental discounted costs**	**Incremental discounted QALYs**	**Cost per QALY gained**
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Company probabilistic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; SoC, standard of care

Table 48: Company base case results (non-bio eligible)

	Discounted costs	**Discounted QALYs**	**Incremental discounted costs**	**Incremental discounted QALYs**	**Cost per QALY gained**
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; SoC, standard of care

As a response to EAG's clarification question B11, the company provided an updated model and the results for the reslizumab eligible population. The base case results of the reslizumab eligible subgroup from company's clarification response has been provided below (Table 49).

Please note that the probabilistic results presented below are based on EAG run, as the probabilistic results were not provided by the company in the clarification response. Furthermore due to differences in inputs, it was not possible to combine the reslizumab analysis with the remaining anti-IL5 biologics analysis.

Table 49: Company base case results (reslizumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Company probabilistic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis

The company performed a number of one-way deterministic sensitivity analyses (CS, Document B, Section B.3.8.2). Where a parametric distribution was assigned, parameters were varied between the 95% confidence/credibility limits. Where data were not otherwise available, parameters were varied by an arbitrary +/-10%. Whilst common practice, this is not ideal as it does not reflect the true state of uncertainty around a parameter. If 'true' uncertainty is greater than +/-10%, this can lead to an incorrect conclusion that the results are insensitive to the parameter.

The company correctly noted that a net monetary benefit framework is a more pragmatic approach to handle negative ICERs generated from sensitivity analysis (and indeed, any analysis), but only presented pairwise comparisons of incremental net monetary benefit for the anti-IL-5 eligible population (which are labelled as 'net monetary benefit'). This prohibits examination of the impact of uncertainty of a parameter on the model conclusions as to which option is the most cost-effective, but nevertheless visual examination does show which parameters lead to the biggest change in pairwise incremental net monetary benefit. It would have been preferable to calculate the net monetary benefit for each of the three comparators, and indicate which was the highest.

Overall, the company identified the most important parameters in the anti-IL-5 eligible popuation to be the 'natural' discontinuation rates of benralizumab and mepolizumab, and relative annual exacerbation rates and their consequences (specifically the proportion leading to hospitalisations) (CS, Document B, Section B.3.8.2.1, Figures 76-78). In the dupilumab-eligible subgroup, the relative exacerbation rate is the most sensitive parameter. In the omalizumab-eligible subgroup, the most sensitive parameters are again the natural discontinuation rate and relative exacerbation rate. In no case does the incremental net monetary benefit cross zero in either the dupilumab or omalizumab-eligible subgroups (implying there is no change as to which treatment is most cost-effective). Finally, in the non-bio eligible subgroup, the conclusions are highly sensitive to all parameters tested, with a number of the transition probabilities and consequences of exacerbations being the most sensitive. This result is expected given the point estimate ICER is just below £30,000/QALY (see Table 48), and thus decision uncertainty is close to its maximum.

5.2.1.1. Threshold analysis

The company also reported the OWSA as a threshold analysis. For the anti-IL-5 eligible subgroup, only pairwise comparisons were made. It was thus not possible to assess the threshold at which the adoption decision changed. However, in the opinion of the EAG, the results are highly unlikely to be sensitive to model parameters. For the dupilumab- and omalizumab-eligible subgroups the model results were insensitive to any of the parameters tested. Finally for the non-bio eligible subgroup, the results were highly sensitive to changes in any of the parameters with the critical values being very close to the base case. As stated above, this is expected due to the point estimate ICER being very close to (the upper range of) NICE's threshold.

The EAG notes that tables 152-156 of the CS (Document B, Section B.3.8.3, pp 289-92) report thresholds outside the logical limits of a number of parameters (e.g., probabilities outside the range [0,1]). This is unnecessary and it would have been perfectly satisfactory for the company to only test such parameters within their logical limits.

Overall, the company's base case results are insensitive to variations in the input parameters tested in the OWSA and threshold analysis in the anti-IL-5, dupilumab- and omalizumab- eligible subgroups, but highly sensitive to variations in the input parameters in the non-bio eligible subgroup.

5.2.2. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis with 10,000 simulations was conducted. Due to the computational time required to run the simulation (in excess of eight hours), the EAG were not able to assess whether this was sufficient to minimise Monte Carlo error. The probabilistic results are reproduced in Table 45 to Table 48 above.

The EAG noted the use of independent beta distributions rather than Dirichlet distributions to model transition probabilities with more than two alternatives. This risks generating probabilities outside the logical limits of [0, 1]. However, ad hoc testing suggested this was not an issue. The EAG also noted a number of minor (inconsequential) errors in the titles of Figures 68, 70 and 72 of the CS: the scatterplots are labelled 'incremental' when the cost/QALY pairs presented are totals accrued in each arm, not increments of one versus another.

5.2.3. Scenario analyses

The company undertook a number of scenario analyses:

- Alternative estimates of asthma death from an exacerbation
- Using alternative sources for patient baseline characteristics
- Alternative discount rate
- Alternative risk of exacerbations

5.2.3.1. Alternative exacerbation-related mortality

The company performed a scenario analysis calibrating all-cause mortality to all-cause mortality in severe asthma patients from a retrospective case-control database analysis published in 2019.[46] This is based on the Echantillon Généraliste des Bénéficiaires (EGB) database, a large (1/97th) representative sample of the medical records of the population of France. Data were extracted for the three year period from 2013-16, which the company notes predates the introduction of most biologic therapies. Therefore they restricted the scenario analysis to the

SoC arm of the non-bio eligible subgroup only. Bourdin et al. (2019)[46] reported 7.1% three-year mortality compared to [redacted]% predicted by the SoC arm in the model. The company further argued that the 7.1% is likely an underestimate due to the more severe population in the model, thus tested a scenario with a 50% higher three-year mortality (10.65%). This reduced the point estimate ICER to [redacted] and £[redacted] respectively.

The EAG notes that the Bourdin[46] data relate to 2013-2016 and drawn from a French dataset which may not be generalisable to England/Wales, and that asthma mortality may have changed since then (the company cite ONS data published in 2019 showing an 8% increase in deaths due to asthma attacks in England and Wales between 2017-18 (CS, Document B, Section B.3.3.4.2). The EAG is minded to agree that the severity of patients in the Bourdin cohort may be somewhat less severe than the population in the model. The EAG also notes that the increased asthma mortality is only applied for the non-bio eligible subgroup. Finally, the EAG refers the committee to comments in Section 4.2.8 of this report where it is the EAG's view that asthma mortality is over-estimated in the model, not underestimated.

5.2.3.2. Alternative baseline characteristics

The company base case baseline characteristics drew on data from the UK Severe Asthma Registry (Jackson et al. 2021), [32] but the company notes this differs from the baseline characteristics of patients enrolled in the NAVIGATOR and SOURCE studies. They therefore conducted a scenario analysis using the trial-specific baseline characteristics. This did not affect the results of the anti-IL5 eligible, dupilumab-eligible or omalizumab-eligible subgroups, but moderately increased the ICER of the non-bio eligible subgroup from £[redacted] to £[redacted] per QALY gained.

5.2.3.3. Alternative discount rates

The company explored a scenario with outcomes discounted at 1.5% rather than the standard 3.5%. This did not affect the results of the anti-IL5 eligible, dupilumab-eligible or omalizumab-eligible subgroups, but moderately reduced the ICER of the non-bio eligible subgroup from £[redacted] to £[redacted] per QALY gained.

5.2.3.4. Alternative comparative exacerbation rates

Anti-IL5 eligible subgroup

The company's base case used a rate ratio of exacerbations derived from the network meta-analysis including patients with EOS ≥300 cells/µL. In the scenario analysis, the company used the NMA including those patients experiencing ≥3 exacerbations in the previous 12 months. Data were not available for mepolizumab, so the company assumed the same rate as for benralizumab. This did not alter the conclusions of the model in the anti-IL5 subgroup.

Dupilumab eligible subgroup

The company's base case used a rate ratio of exacerbations derived from the network meta-analysis including patients with EOS <300 cells/µL. Three alternative scenarios were considered:

- FeNO ≥25 ppb subgroup NMA data
- ≥3 Exacerbations in last 12 months subgroup NMA data
- ≥150 cells/µL subgroup NMA data

None of the scenarios altered the conclusions of the model in the dupilumab subgroup.

Omalizumab subgroup and non-biologic eligible subgroup

The company did not present scenario analyses exploring different risks of exacerbation in the omalizumab or non-bio eligible subgroups.

Reslizumab-eligible subgroup

The company presented a scenario analyses for the reslizumab eligible subgroup in the clarification response (B11) with the relative annual exacerbation rate sourced from ≥3 exacerbations in the prior 12 months subgroup NMA. However, this scenario did not alter the conclusion of the base case.

5.3. Model validation and face validity check

The CS stated that interim QC was conducted by the developers and a third party during development of the model, as well as by the company itself.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the EAG believes are more plausible.

This section is organised as follows:

- Section 6.1 details the impact of errors identified in the EAG's verification and validation of the executable model.
- Section 6.2 details a series of EAG's scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG.
- In Section 6.3, the EAG base-case is presented (in an incremental as well as cumulative manner) based on EAG's preferred assumptions.

6.1. EAG corrections and adjustments to the company's base case model

Besides several minor errors in the navigation macros and labelling, EAG noted the following issues with the CS and the clarification response:

- The probabilistic and deterministic results for the omalizumab eligible subgroup were identical. This is likely to be a cut-and-paste error and did not have any impact on the model results.
- The list price of reslizumab (225 mg) included in the company's clarification response for question B11 was £1,124.97 whereas the list price included in the model was £1,249.96. EAG identified the list price mentioned in the clarification response to be correct (based on 2x100mg+1x25mg) and subsequently updated the cost of reslizumab in the model.
- The PSA was not functional for the reslizumab eligible subgroup in the updated model (including reslizumab) provided by the company as part of the clarification response. In the EAG model, therefore, this was fixed by incorporating the reslizumab data into the original company submitted model as part of Anti-IL5 subgroup (however, reslizumab eligible subgroup was run separately owing to differences in the inputs versus other anti-IL5 treatments).

Please note that the corrections mentioned above only impacted the reslizumab eligible subgroup.

Table 50: EAG-corrected company base case results (reslizumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	-
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Company probabilistic base case					
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]			-
Reslizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Fully incremental results presented.

Abbreviations: QALYs, quality adjusted life years; SoC Standard of Care

6.2. Exploratory and sensitivity analyses undertaken by the EAG

As noted throughout the report, the EAG conducted several scenario analyses to explore uncertainty surrounding certain model parameters and assumptions. The scenario analyses are listed below and the associated results are presented in Section 6.2.10.

6.2.1. No difference in utilities for controlled and uncontrolled exacerbations

As described in Section 4.2.2, to assess the uncertainty around the model structure (i.e., classifying exacerbations into controlled and uncontrolled) the EAG conducted an analysis where the utilities for controlled and uncontrolled exacerbations were assumed to be the same. This scenario impacts all the subgroups considered in the model.

6.2.2. Asthma mortality risk re-estimated for people <75 years of age

This assumption used updated asthma mortality data (2020) from ONS and re-estimated the mortality risk for people <75 years of age in line with the finding from HSE 2018 asthma report i.e., approximately one-quarter of asthma deaths occur in adults aged <75 years. The per-cycle probabilities of death following an exacerbation used in the EAG model have been provided in

Table 42 (please refer to Section 4.2.8 for further details). This scenario impacts all the subgroups considered in the model.

6.2.3. No additional utility gain for being on biological treatment

The company base case included utility gain for people being on biological treatment which was not attached specifically to any health state in the model but attributed to elements of HRQoL which were not captured within the model structure. Given the evidence to support this additional utility gain was less robust and uncertain, EAG conducted an analysis without including the biological treatment utility gain as described in Section 4.2.7. This scenario also impacts all the subgroups considered in the model.

6.2.4. Exacerbation split (OCS burst/ED visit/Hospitalisation) assumed to be the same as tezepelumab for other biologics

Company’s modelled base case applied relative effects of exacerbations and hospitalisations simultaneously in an incommensurate manner as mentioned in Section 3.3.3 and detailed further in Section 4.2.6.4, which is likely to overestimate the treatment effect of tezepelumab vs other biologics in terms of hospitalisations. To address this, EAG performed an analysis assuming same split of exacerbations as tezepelumab for other biologics thereby preventing the simultaneous application of multiple relative effects. Please note that this change impacts all the subgroups except the non-bio eligible subgroup.

6.2.5. Relative exacerbation rate for dupilumab derived from High EOS ≥150 subgroup NMA

The company’s base case used relative risk of exacerbations derived from the NMA including patients with EOS <300 cells/µL, while the high EOS ≥150 subgroup NMA data derived relative exacerbation rate was tested in company’s scenario analysis, as noted in Section 5.2.3.4. However, clinical opinion to EAG indicated that due to the positioning of dupilumab in UK clinical practice and the ‘true’ EOS count threshold used of ≥150, it would be preferable to draw on the EOS ≥150 subgroup in the base case. Therefore, EAG conducted an analysis by considering the relative risk of exacerbations based on high EOS ≥150 subgroup NMA data in the base case for dupilumab. Please note that this analysis only impacted the results for dupilumab eligible subgroup in the model.

6.2.6. No asthma mortality risk

The EAG performed a no asthma mortality scenario to reflect the observation in the tezepelumab pivotal trials (as there were no deaths observed in the trials). Though this scenario is unlikely to be realistic (owing to several challenges associated with asthma management), it could provide some insights into the uncertainty associated with the asthma mortality inputs and the sensitivity of the model results to those inputs (as zero mortality scenario is well beyond the typical bounds tested within the deterministic sensitivity analysis).

It is to be noted that because the model results for all subgroups are sensitive to asthma mortality inputs, a substantial increase in ICER was noted.

6.2.7. Alternative transition probabilities

6.2.7.1. Post-assessment TPs assumed to be the same as pre-assessment TPs

This scenario helps to address the uncertainty associated with the post-assessment TPs (after 52 weeks) arising from the fact that it is based on an indeterminate definition of response assumed in the model (as mentioned in Section 4.2.6.2). This scenario is applicable to all subgroups except the dupilumab eligible subgroup (as tezepelumab TPs are the same pre- and post- assessment for dupilumab eligible population as per CS, Document B, Table 102). As expected, this scenario of constant TPs resulted in lesser proportion of patients ending up in controlled asthma state in the long-term leading to a reduction in total QALYs for all treatments. However, the increase or decrease in incremental QALYs depend on the magnitude of reduction in individual treatment arms.

6.2.7.2. TPs for controlled exacerbation to asthma control assumed to be the same as TPs for uncontrolled exacerbation to asthma control

This EAG scenario facilitates testing the uncertainty associated with the probabilities of transitioning from controlled and uncontrolled exacerbation states to asthma control states, as detailed in Section 4.2.6.3. Additionally, this scenario could be seen as an extension of the EAG base case change: ‘no difference in utilities for controlled and uncontrolled exacerbations’, which is detailed further in Section 6.2.3. This scenario impacted all the subgroups and resulted in reduction in total QALYs for all treatments, however, the increase or decrease in incremental QALYs depend on the magnitude of reduction in individual treatment arms.

6.2.7.3. TPs for asthma control states based on ACQ cut-off of 1 (instead of 1.5)

As elaborated in Section 4.2.6.1, this scenario explores the impact of alternative ACQ cut-off value of 1 as the company model used cut-off (1.5) classifies some of the partially controlled cohort as controlled. As EAG was unable to recalculate the TPs using the alternative cut-off (owing to the unavailability of required IPD data from trials) a scenario analysis approximating this by multiplying relevant transition probabilities (TPs of asthma control states) by the PPV (0.88) was conducted. Like the previous transition probabilities related scenarios, this would also result in reduction in total QALYs of all treatments as more patients transition to uncontrolled and exacerbation states.

6.2.8. Response evaluation for omalizumab at 16 weeks (instead of 52 weeks)

The company base case model assessed the response of all biologic treatments at 52 weeks, however, for omalizumab in clinical practice the response evaluation is typically conducted at 16 weeks. This scenario therefore explores the impact of alternative response assessment timepoint for omalizumab. This scenario only impacted the omalizumab eligible subgroup and resulted in slight increase in the ICER primarily due to reduction in QALY loss.

6.2.9. Shorter time horizon (20 years)

In this scenario, the EAG explored the impact of shorter time horizon (20 years) on the cost-effectiveness of the treatments as a proxy way of testing the uncertainty associated with optimal treatment duration of biologic treatments in severe asthma. As the treatment QALY decreases with a shorter time horizon, an increase in ICER was observed as expected. This scenario affected all the subgroups.

6.2.10. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.9. Each change has been made individually. The results of the EAG's exploratory analyses are provided in Table 51.

The key drivers based on the EAG's exploratory analyses were found to be the updated estimate for asthma exacerbation related mortality for people <75 years of age, no additional utility gain assumption for being on biological treatment, the assumption of same exacerbation split as tezepelumab for other biologic and the relative risk of exacerbations based on high EOS ≥150 subgroup NMA for dupilumab.

Table 51: EAG's exploratory analyses

Preferred assumption	**Section in EAG report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
Anti-IL5 eligible^ (Comparators: Mepolizumab+SoC, Benralizumab+SoC)					
Company base case	*5.1.1*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	-
Benralizumab + SoC		[redacted]	[redacted]	Dominated	-
No difference in utilities: Controlled vs. Uncontrolled exacerbations	*6.2.1*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-2%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-4%*
Re-estimated asthma mortality for people <75 years	*6.2.2*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*75%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*339%*
No additional utility gain for being on biological treatment	*6.2.3*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*18%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*4%*
Exacerbation split same as TEZ for other biologics	*6.2.4*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*6%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*17%*
No asthma mortality	*6.2.6*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*152%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*>1000%*
Alternative transition probabilities					
a. Post-response assessment TP =	*6.2.7.1*				

Preferred assumption		**Section in EAG report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
	Pre-response assessment TP					
	Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*3%*
	Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-28%*
b.	Con Ex TP = Uncon Ex TP	*6.2.7.2*				
	Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-7%*
	Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-16%*
c.	Asthma control state TP based on ACQ cut off =1 (company base case * 0.88)	*6.2.7.3*				
	Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-1%*
	Benralizumab + SoC		[redacted]	[redacted]	Dominated	*1%*
Time horizon = 20 years		*6.2.9*				
Mepolizumab + SoC			[redacted]	[redacted]	Dominated	*47%*
Benralizumab + SoC			[redacted]	[redacted]	Dominated	*36%*
Reslizumab eligible (Comparator: Reslizumab+SoC)						
ERG corrected Company base case		*6.1*	[redacted]	[redacted]	Dominated	-
No difference in utilities: Controlled vs. Uncontrolled exacerbations		*6.2.3*	[redacted]	[redacted]	Dominated	*-4%*
Re-estimated asthma mortality for people <75 years		*6.2.2*	[redacted]	[redacted]	Dominated	*591%*
No additional utility gain for being on biological treatment		*6.2.3*	[redacted]	[redacted]	Dominated	*3%*
Exacerbation split same as TEZ for other biologics		*6.2.4*	[redacted]	[redacted]	Dominated	*0%*
No asthma mortality		*6.2.6*	[redacted]	[redacted]	Dominated	*>1000%*

Preferred assumption	**Section in EAG report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
Alternative transition probabilities					
a. Post-response assessment TP = Pre-response assessment TP	*6.2.7.1*	[redacted]	[redacted]	Dominated	*-51%*
b. Con Ex TP = Uncon Ex TP	*6.2.7.2*	[redacted]	[redacted]	Dominated	*-11%*
c. Asthma control state TP based on ACQ cut off =1 (company base case * 0.88)	*6.2.7.3*	[redacted]	[redacted]	Dominated	*-1%*
Time horizon = 20 years	*6.2.9*	[redacted]	[redacted]	Dominated	*33%*
Dupilumab eligible (Comparator: Dupilumab+SoC)					
Company base case	*5.1.1*	[redacted]	[redacted]	Dominated	-
No difference in utilities: Controlled vs. Uncontrolled exacerbations	*6.2.1*	[redacted]	[redacted]	Dominated	*-1%*
Re-estimated asthma mortality for people <75 years	*6.2.2*	[redacted]	[redacted]	Dominated	*173%*
No additional utility gain for being on biological treatment	*6.2.3*	[redacted]	[redacted]	Dominated	*3%*
Exacerbation split same as TEZ for other biologics	*6.2.4*	[redacted]	[redacted]	Dominated	*71%*
Relative exacerbation rate for dupilumab derived from High EoS ≥150 NMA subgroup	*6.2.5*	[redacted]	[redacted]	Dominated	*101%*
No asthma mortality	*6.2.6*	[redacted]	[redacted]	Dominated	*>1000%*
Alternative transition probabilities					
a. Post-response assessment TP = Pre-response assessment TP	*6.2.7.1*	[redacted]	[redacted]	Dominated	*0%*
b. Con Ex TP = Uncon Ex TP	*6.2.7.2*	[redacted]	[redacted]	Dominated	*-8%*

Preferred assumption	**Section in EAG report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
c. Asthma control state TP based on ACQ cut off =1 (company base case * 0.88)	*6.2.7.3*	[redacted]	[redacted]	Dominated	*1%*
Time horizon = 20 years	*6.2.9*	[redacted]	[redacted]	Dominated	*55%*
Omalizumab eligible (Comparator: Omalizumab+SoC)					
Company base case	*5.1.1*	[redacted]	[redacted]	Dominated	-
No difference in utilities: Controlled vs. Uncontrolled exacerbations	*6.2.1*	[redacted]	[redacted]	Dominated	*-2%*
Re-estimated asthma mortality for people <75 years	*6.2.2*	[redacted]	[redacted]	Dominated	*254%*
No additional utility gain for being on biological treatment	*6.2.3*	[redacted]	[redacted]	Dominated	*3%*
Exacerbation split same as TEZ for other biologics	*6.2.4*	[redacted]	[redacted]	Dominated	*12%*
No asthma mortality	*6.2.6*	[redacted]	[redacted]	Dominated	*>1000%*
Alternative transition probabilities					
a. Post-response assessment TP = Pre-response assessment TP	*6.2.7.1*	[redacted]	[redacted]	Dominated	*-26%*
b. Con Ex TP = Uncon Ex TP	*6.2.7.2*	[redacted]	[redacted]	Dominated	*-14%*
c. Asthma control state TP based on ACQ cut off =1 (company base case * 0.88)	*6.2.7.3*	[redacted]	[redacted]	Dominated	*0%*
Response assessment of omalizumab at 16 weeks	*6.2.8*	[redacted]	[redacted]	Dominated	*8%*
Time horizon = 20 years	*6.2.9*	[redacted]	[redacted]	Dominated	*51%*
Non-bio eligible, 3+ exacerbations or mOCS (Comparator: SoC)					
Company base case	*5.1.1*	[redacted]	[redacted]	[redacted]	-
No difference in utilities: Controlled vs.	*6.2.1*	[redacted]	[redacted]	[redacted]	*0%*

Preferred assumption	**Section in EAG report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
Uncontrolled exacerbations					
Re-estimated asthma mortality for people <75 years	*6.2.2*	[redacted]	[redacted]	[redacted]	*63%*
No additional utility gain for being on biological treatment	*6.2.3*	[redacted]	[redacted]	[redacted]	*60%*
No asthma mortality	*6.2.6*	[redacted]	[redacted]	[redacted]	*121%*
Alternative transition probabilities					
a. Post-response assessment TP = Pre-response assessment TP	*6.2.7.1*	[redacted]	[redacted]	[redacted]	*16%*
b. Con Ex TP = Uncon Ex TP	*6.2.7.2*	[redacted]	[redacted]	[redacted]	*-10%*
c. Asthma control state TP based on ACQ cut off =1 (company base case * 0.88)	*6.2.7.3*	[redacted]	[redacted]	[redacted]	*0%*
Time horizon = 20 years	*6.2.9*	[redacted]	[redacted]	[redacted]	*30%*

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, Transition probabilities; Con Ex, Controlled exacerbations; Uncon Ex, Uncontrolled exacerbations; Soc, Standard of Care

*ERG corrected company base case where applicable

^Fully incremental analysis results are presented for Anti-IL5 eligible subgroup

6.3. EAG's preferred assumptions

This section presents the results based on EAG preferred assumptions for the base case. The results below present both the incremental and cumulative impact of EAG preferences.

As part of the preferred base case, the EAG considered the following assumptions:

- No difference in utilities for controlled and uncontrolled exacerbations (applicable to all subgroups)
- Asthma mortality risk re-estimated for people <75 years of age (applicable to all subgroups)

- No additional utility gain for being on biological treatment (applicable to all subgroups)
- Exacerbation split (OCS burst/ED visit/Hospitalisation) assumed to be the same as tezepelumab for other biologics (applicable to Anti-IL5, reslizumab, dupilumab and omalizumab eligible subgroups)
- Relative exacerbation rate for dupilumab derived from High EOS ≥150 subgroup NMA (applicable to only dupilumab eligible subgroup)

The cumulative impact of these changes in the EAG base case for each subgroup has been described below.

- **Non-bio eligible subgroup**: The incremental QALYs decreased considerably when compared to the company base case with the greatest reduction in incremental QALYs occurring due to re-estimated asthma exacerbation related mortality risk for people <75 years of age followed by the assumption of no utility gain for being on biological treatment. There was a slight decrease observed with the incremental costs. The net impact was an increased ICER primarily driven by the reduction in the incremental QALYs. As shown in Table 56, the add-on tezepelumab treatment resulted in an incremental cost of [redacted] and incremental QALYs of [redacted] when compared with SoC alone, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted] and incremental QALYs of [redacted], which were aligned closely with that of the deterministic analysis. The CEAC indicated that the probability of tezepelumab being cost-effective reduced to 0.19% (based on 10000 PSA simulations) at a willingness-to-pay threshold of £30,000 (please see Appendix 1 for further details).
- **Reslizumab eligible subgroup:** The QALY loss decreased considerably when compared to the company base case with the greatest reduction in QALY loss occurring due to re-estimated asthma exacerbation related mortality risk for people <75 years of age. There was a slight increase observed with the incremental costs. As shown in Table 53, the add-on reslizumab treatment was dominated with an incremental cost of [redacted] and QALY loss of [redacted] when compared with add-on tezepelumab treatment, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted]and QALY loss of [redacted]. Please see Appendix 1 for further details on the PSA and CEAC.

- **Dupilumab eligible subgroup:** The QALY loss decreased considerably when compared to the company base case with the greatest reduction in QALY loss occurring due to re-estimated asthma exacerbation related mortality risk for people <75 years of age followed by the assumption of no utility gain for being on biological treatment. There was a slight increase observed with the incremental costs. As shown in Table 54, the add-on dupilumab treatment was dominated with an incremental cost of [redacted] and QALY loss of [redacted] when compared with add-on tezepelumab treatment, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted] and QALY loss of [redacted]. Please see Appendix 1 for further details on the PSA and CEAC.
- **Omalizumab eligible subgroup:** The QALY loss decreased considerably when compared to the company base case with the greatest reduction in QALY loss occurring due to re-estimated asthma exacerbation related mortality risk for people <75 years of age followed by the assumption of no utility gain for being on biological treatment. There was a slight increase observed with the incremental costs. As shown in Table 54, the add-on omalizumab treatment was dominated with an incremental cost of [redacted] and QALY loss of [redacted] when compared with add-on tezepelumab treatment, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted] and QALY loss of [redacted]. Please see Appendix 1 for further details on the PSA and CEAC.
- **Anti-IL5 eligible subgroup:** Based on a fully incremental analysis, the QALY loss decreased considerably when compared to the company base case for both benralizumab and mepolizumab with the greatest reduction in QALY loss occurring due to re-estimated asthma exacerbation related mortality risk for people <75 years of age followed by the assumption of no utility gain for being on biological treatment. There was a slight increase observed with the incremental costs. As shown in Table 52, the add-on mepolizumab treatment was dominated with an incremental cost of [redacted] and QALY loss of [redacted] when compared with add-on tezepelumab treatment, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted] and QALY loss of [redacted]. Similarly, the add-on benralizumab treatment was dominated with an incremental cost of [redacted] and QALY loss of [redacted] when compared with add-on tezepelumab treatment, in the deterministic analysis. The probabilistic analysis resulted in an incremental cost of [redacted] and QALY loss of [redacted]. Please see Appendix 1 further details on the PSA and CEAC. Please note that the accuracy of probabilistic results for the EAG base case could be

improved further with a revised 5x5 variance-covariance matrix (without biological treatment utility) for the utility equation (currently the biological treatment utility coefficient has been set to zero both in deterministic and probabilistic analysis though with a 6x6 variance-covariance matrix). Furthermore, the results presented here would likely change when the comparator PAS discounts are considered (currently the PAS price is considered only for tezepelumab).

Table 52: EAG's preferred model assumptions (anti-IL5 eligible)

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No difference in utilities for controlled and uncontrolled exacerbations						
Tezepelumab (PAS price) + SoC	*6.2.1*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Asthma mortality re-estimated for people aged <75 years						
Tezepelumab (PAS price) + SoC	*6.2.2*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No additional utility gain for being on biological treatment						
Tezepelumab (PAS price) + SoC	*6.2.3*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Exacerbations split (OCS burst/ED visit/Hosp) same as TEZ for other biologics / Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.2.4*	[redacted]	[redacted]	-	-	
Mepolizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**
Benralizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**
Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	-	[redacted]	[redacted]	-	-	

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
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 53: EAG's preferred model assumptions (reslizumab eligible)

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
EAG corrected company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No difference in utilities for controlled and uncontrolled exacerbations						
Tezepelumab (PAS price) + SoC	*6.2.1*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Asthma mortality re-estimated for people aged <75 years						
Tezepelumab (PAS price) + SoC	*6.2.2*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No additional utility gain for being on biological treatment						
Tezepelumab (PAS price) + SoC	*6.2.3*	[redacted]	[redacted]	-	-	-
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Exacerbations split (OCS burst/ED visit/Hosp) same as TEZ for other biologics^ /						

Preferred assumption	**Section in EAG report**	**Total costs**	**Total QALYs**	**Incremental cost**	**Incremental QALYs**	**ICER £/QALY**
Cumulative (deterministic)						
Tezepelumab (PAS price) + SoC	*6.2.4*	[redacted]	[redacted]	**-**	**-**	**-**
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**
Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC		[redacted]	[redacted]			
Reslizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**

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

^Note: Tezepelumab hospitalisation rate for resli-eligible population is zero. Hence, the split remains the same leading to same results as previous scenario.

Table 54: EAG's preferred model assumptions (dupilumab eligible)

Preferred assumption	**Section in EAG report**	**Total costs**	**Total QALYs**	**Incremental cost**	**Incremental QALYs**	**ICER £/QALY**
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No difference in utilities for controlled and uncontrolled exacerbations						
Tezepelumab (PAS price) + SoC	*6.2.1*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]6	Dominated
Asthma mortality re-estimated for people aged <75 years						
Tezepelumab (PAS price) + SoC	*6.2.2*	[redacted]	[redacted]	-	-	-

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No additional utility gain for being on biological treatment						
Tezepelumab (PAS price) + SoC	*6.2.3*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Exacerbations split (OCS burst/ED visit/Hosp) same as TEZ for other biologics						
Tezepelumab (PAS price) + SoC	*6.2.4*	[redacted]	[redacted]	-	-	-
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Relative exacerbation rate for dupilumab based on High EoS >150 / **Cumulative (deterministic)**						
Tezepelumab (PAS price) + SoC	*6.2.5*	[redacted]	[redacted]	**-**	**-**	**-**
Dupilumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**
Cumulative (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 55: EAG's preferred model assumptions (omalizumab eligible)

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Company base-case						

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No difference in utilities for controlled and uncontrolled exacerbations						
Tezepelumab (PAS price) + SoC	*6.2.1*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Asthma mortality re-estimated for people aged <75 years						
Tezepelumab (PAS price) + SoC	*6.2.2*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
No additional utility gain for being on biological treatment						
Tezepelumab (PAS price) + SoC	*6.2.3*	[redacted]	[redacted]	-	-	-
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Exacerbations split (OCS burst/ED visit/Hosp) same as TEZ for other biologics / **Cumulative (deterministic)**						
Tezepelumab (PAS price) + SoC	*6.2.4*	[redacted]	[redacted]	**-**	**-**	**-**
Omalizumab + SoC		[redacted]	[redacted]	[redacted]	[redacted]	**Dominated**
Cumulative (probabilistic)						
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 56: EAG's preferred model assumptions (non-bio eligible)

Preferred assumption	Section in EAG report	Total costs	Total QALYs	Incremental cost	Incremental QALYs	ICER £/QALY
Company base-case						
Tezepelumab (PAS price) + SoC	*5.1.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-
No difference in utilities for controlled and uncontrolled exacerbations						
Tezepelumab (PAS price) + SoC	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-
Asthma mortality re-estimated for people aged <75 years						
Tezepelumab (PAS price) + SoC	*6.2.2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-
No additional utility gain for being on biological treatment / **Cumulative (deterministic)**						
Tezepelumab (PAS price) + SoC	*6.2.3*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC		[redacted]	[redacted]	-	-	-
Cumulative (probabilistic)						
Tezepelumab (PAS price) + SoC	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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

6.4. Conclusions of the cost-effectiveness section

Based on EAG's analyses, in the non-biologic eligible subgroup, add-on tezepelumab treatment to SoC when compared to SoC alone resulted in an ICER of [redacted] based on additional cost of [redacted] over SoC for additional QALY gain of [redacted] (lifetime horizon), in the deterministic analysis. The probabilistic analysis also resulted in similar QALY gain ([redacted] for an additional cost of [redacted] resulting in an ICER of [redacted]. This is substantially higher than the willingness-to-pay threshold of £30k/QALY. Therefore, based on EAG preferred assumptions for the base case, add-on tezepelumab treatment does not seem to be a cost-effective treatment option for the non-bio eligible subgroup who either had 3 or more exacerbations in the previous year or who are on maintenance OCS.

In contrast, add-on tezepelumab dominated the other treatment options (based on comparator list prices) in the anti-IL-5 eligible (those currently treated with benralizumab and mepolizumab), dupilumab eligible, reslizumab eligible and omalizumab eligible subpopulations. However, EAG's exploratory analyses results indicated that there is high uncertainty associated with the comparison of tezepelumab versus other biologics and depending upon the assumptions made in the modelling huge variation in QALY gains were observed in these populations.

The key drivers based on EAG's analyses were found to be the updated estimate for asthma exacerbation related mortality for people <75 years of age and no additional utility gain assumption for being on biological treatment for non-bio eligible as well as bio eligible (anti-IL5, dupilumab, reslizumab and omalizumab eligible) subgroups. Additionally, for the bio-eligible subgroups the assumption of exacerbation split to be the same as tezepelumab for other biologics also had considerable impact. Especially, for the dupilumab eligible subgroup this assumption of same exacerbation split and the relative risk of exacerbations based on High EOS ≥150 subgroup NMA have had a larger impact on the cost-effectiveness results. Further, EAG would like to note that the scenarios conducted to assess the uncertainty associated with structuring the exacerbations into controlled and uncontrolled in the EAG model, should only be seen as a starting point towards addressing the structural uncertainty associated with it as the true impact remains unknown unless a single exacerbation state or equivalent assumptions have been fully implemented.

7. END OF LIFE

The CS contains no mention of tezepelumab in terms of an end of life treatment. As average life expectancy in this population is notably longer than two years, and the survival extension (measured as the mean incremental, undiscounted LY gain) is less than three months, NICE's end-of-life considerations are not applicable to this appraisal and are therefore not discussed further.

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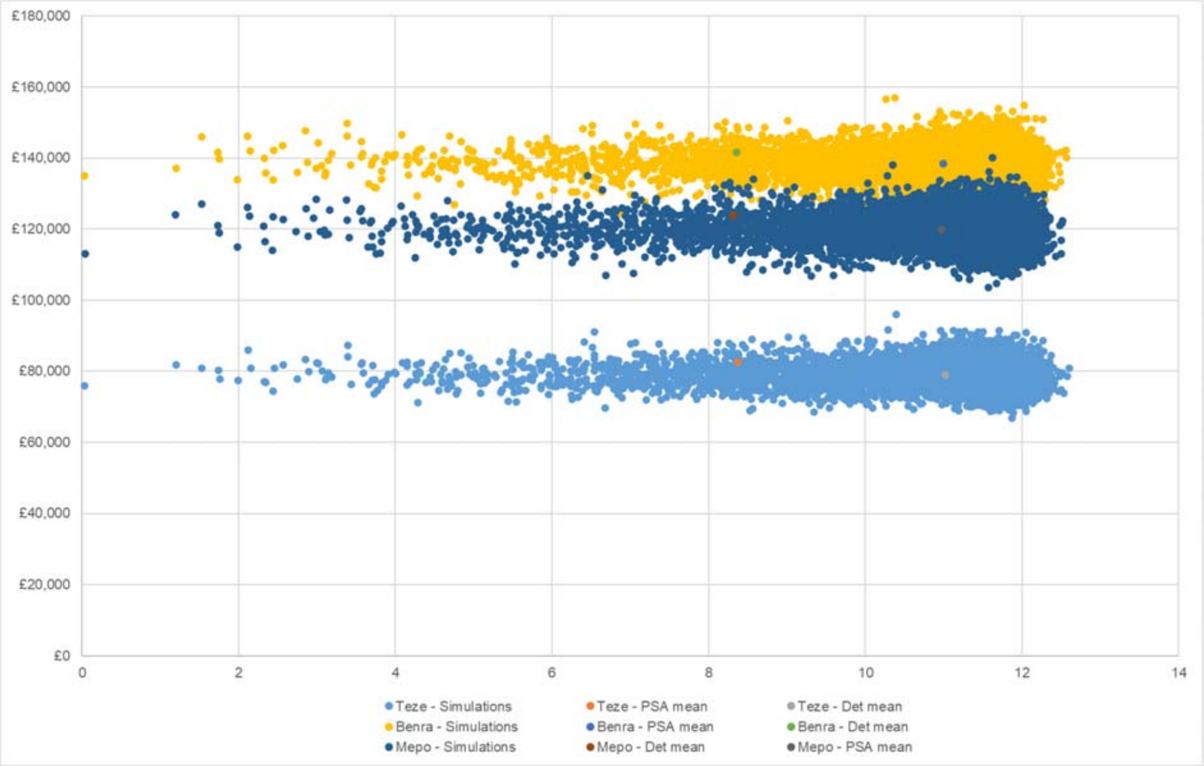
Appendix 1: EAG base case assumptions: CE plane and CE frontier

This appendix presents the CE plane and the CE frontier based on the PSA simulations for the EAG base case assumptions for all the subgroups considered in the model. The results are based on 10,000 PSA simulations.

Anti-IL5 eligible subgroup

Figure 13: Incremental cost-effectiveness scatter plot (anti-IL-5 eligible)



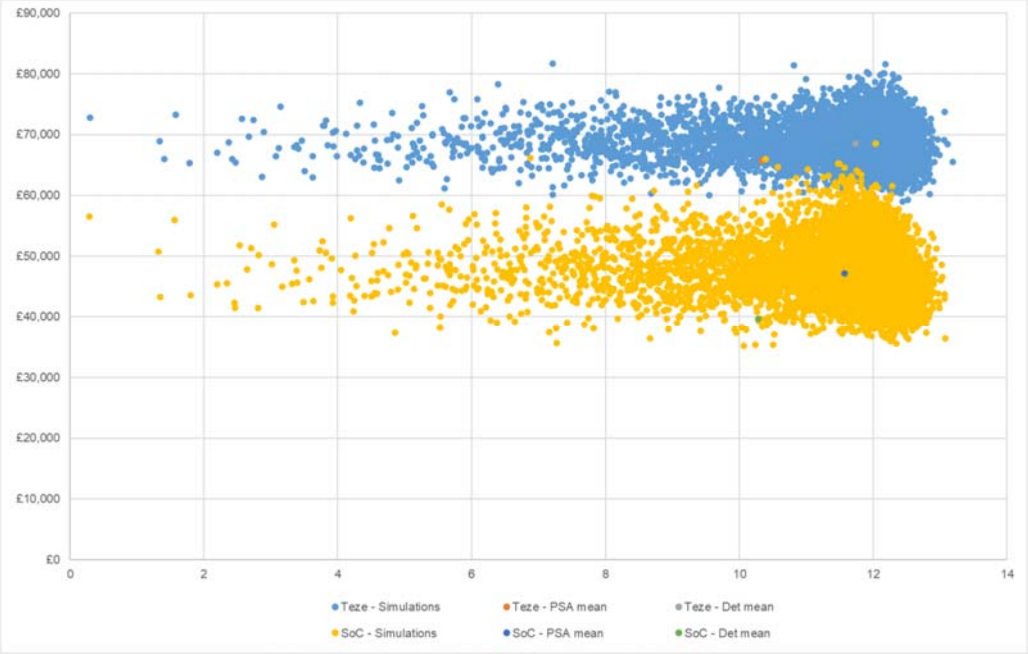
Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; PSA, probabilistic sensitivity analysis.

Figure 14: Cost-effectiveness frontier (anti-IL-5 eligible)

Abbreviations: CE, cost-effectiveness; IL, interleukin.

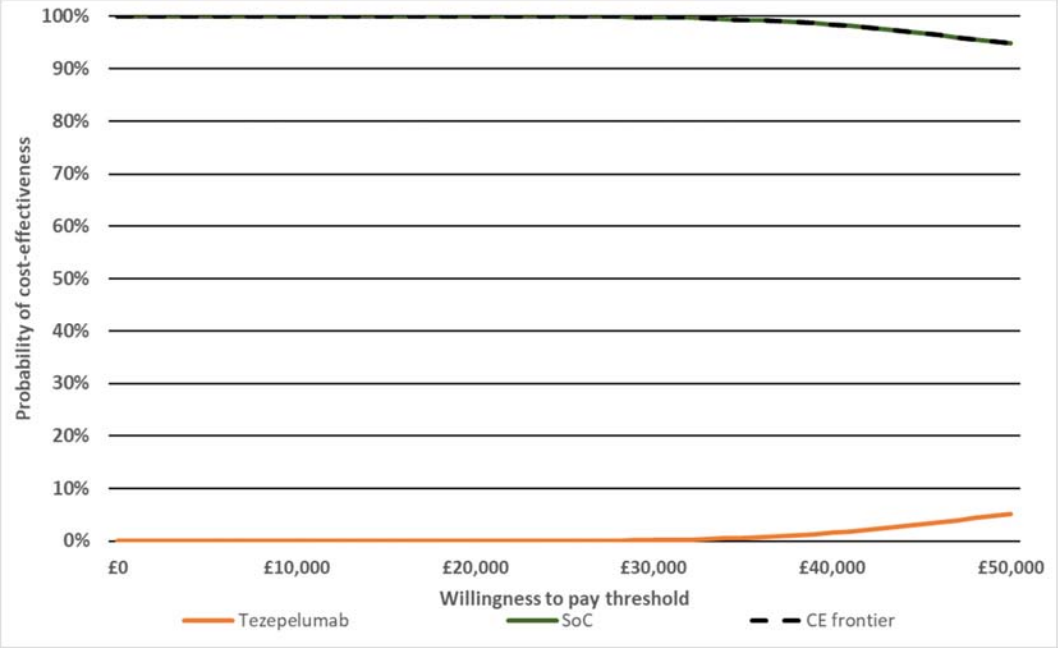
Non-bio eligible subgroup

Figure 15: Incremental cost-effectiveness scatter plot (non-bio eligible [3+ exacs OR mOCS])



Abbreviations: exacs, exacerbations; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroid treatment; PSA, probabilistic sensitivity analysis; SoC, standard of care.

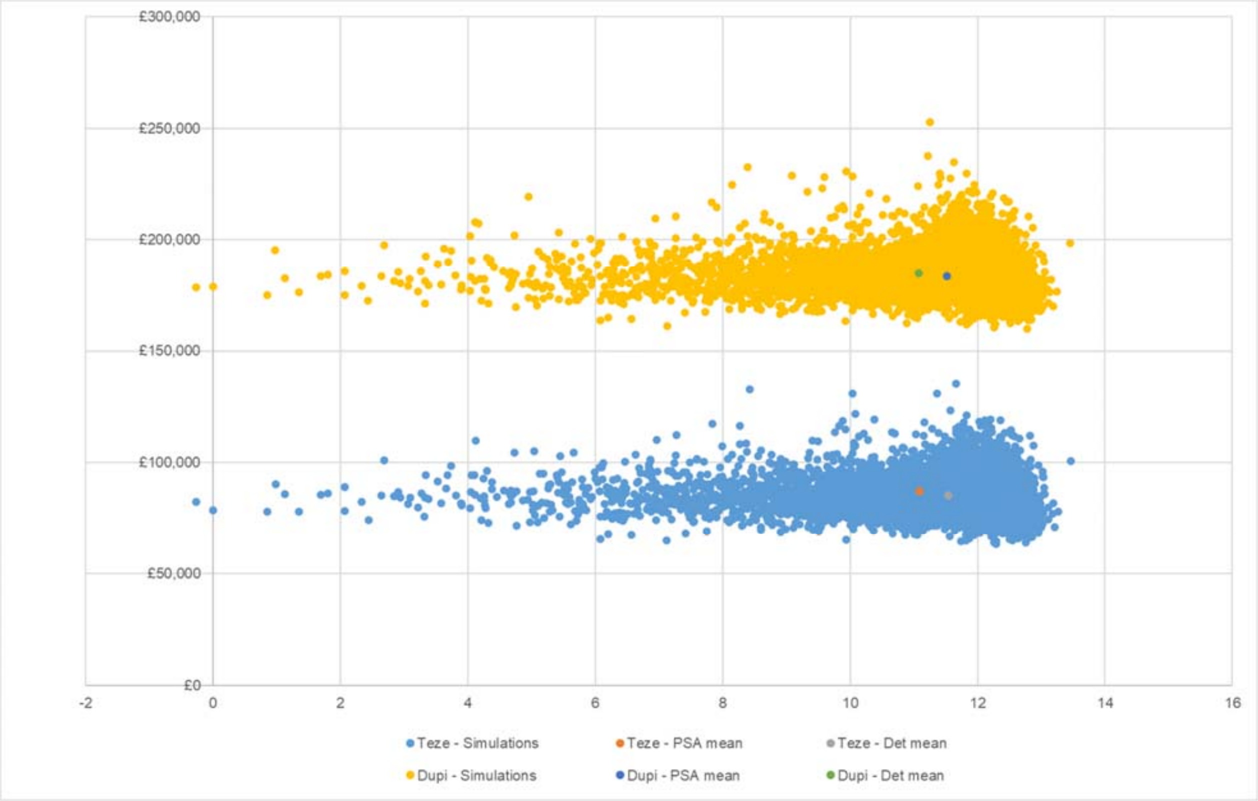
Figure 16: Cost-effectiveness frontier (non-bio eligible [3+ exacs OR mOCS])



Abbreviations: CE, cost-effectiveness; exacs, exacerbations; mOCS, maintenance oral corticosteroid treatment; SoC, standard of care.

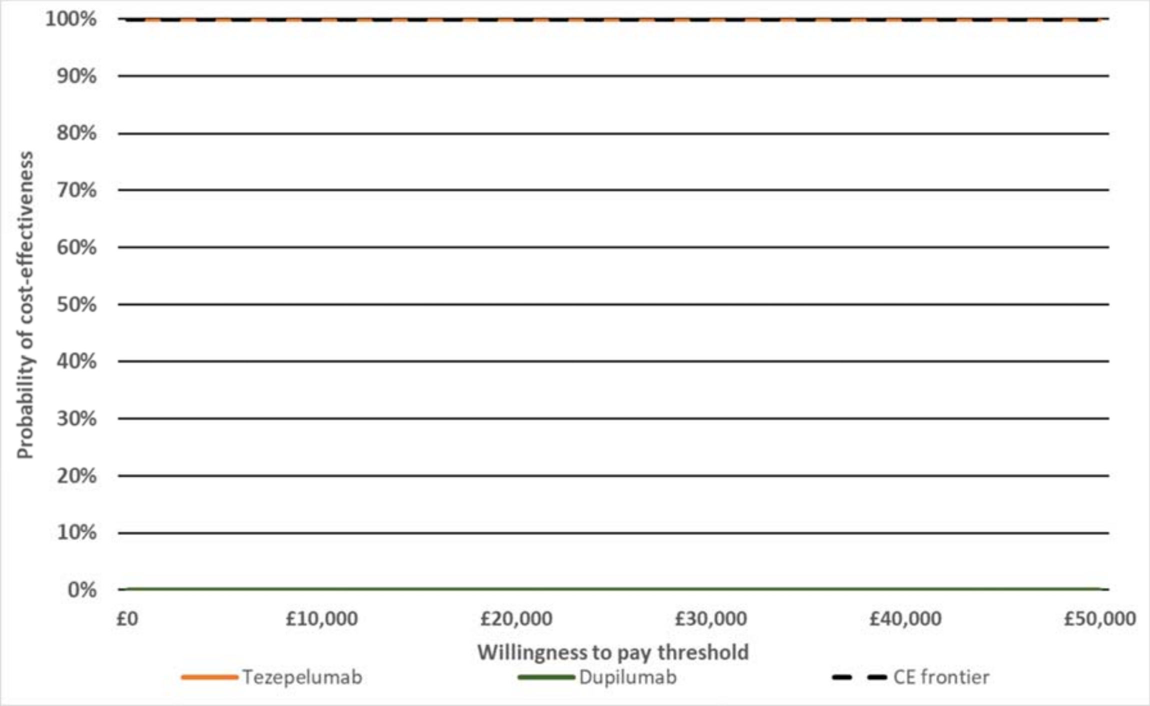
Dupilumab-eligible subgroup

Figure 17: Incremental cost-effectiveness scatter plot (dupilumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

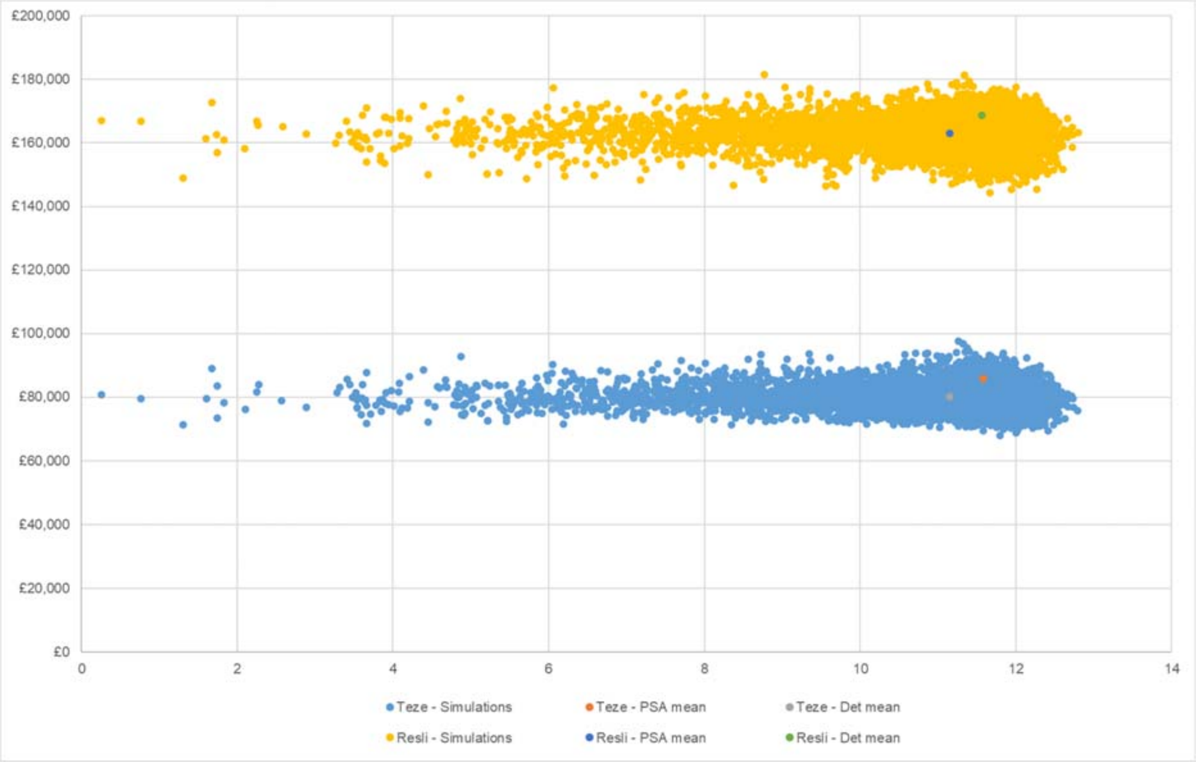
Figure 18: Cost-effectiveness frontier (dupilumab eligible)



Abbreviations: CE, cost-effectiveness.

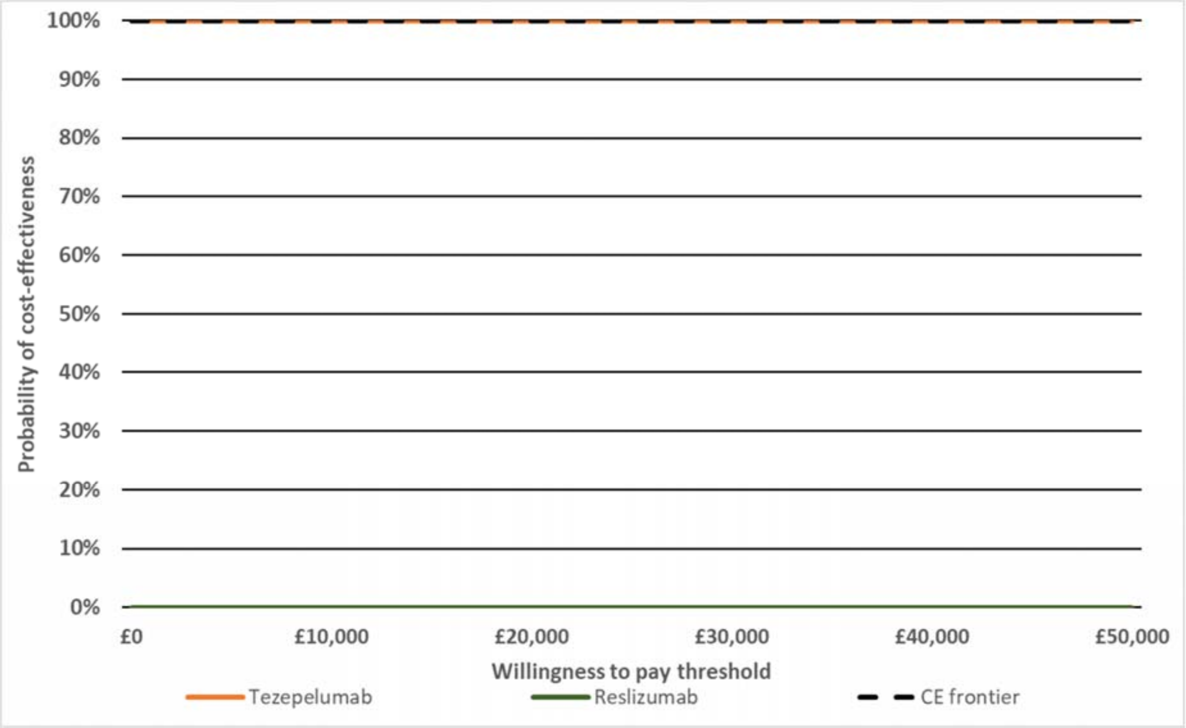
Reslizumab-eligible subgroup

Figure 19: Incremental cost-effectiveness scatter plot (reslizumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

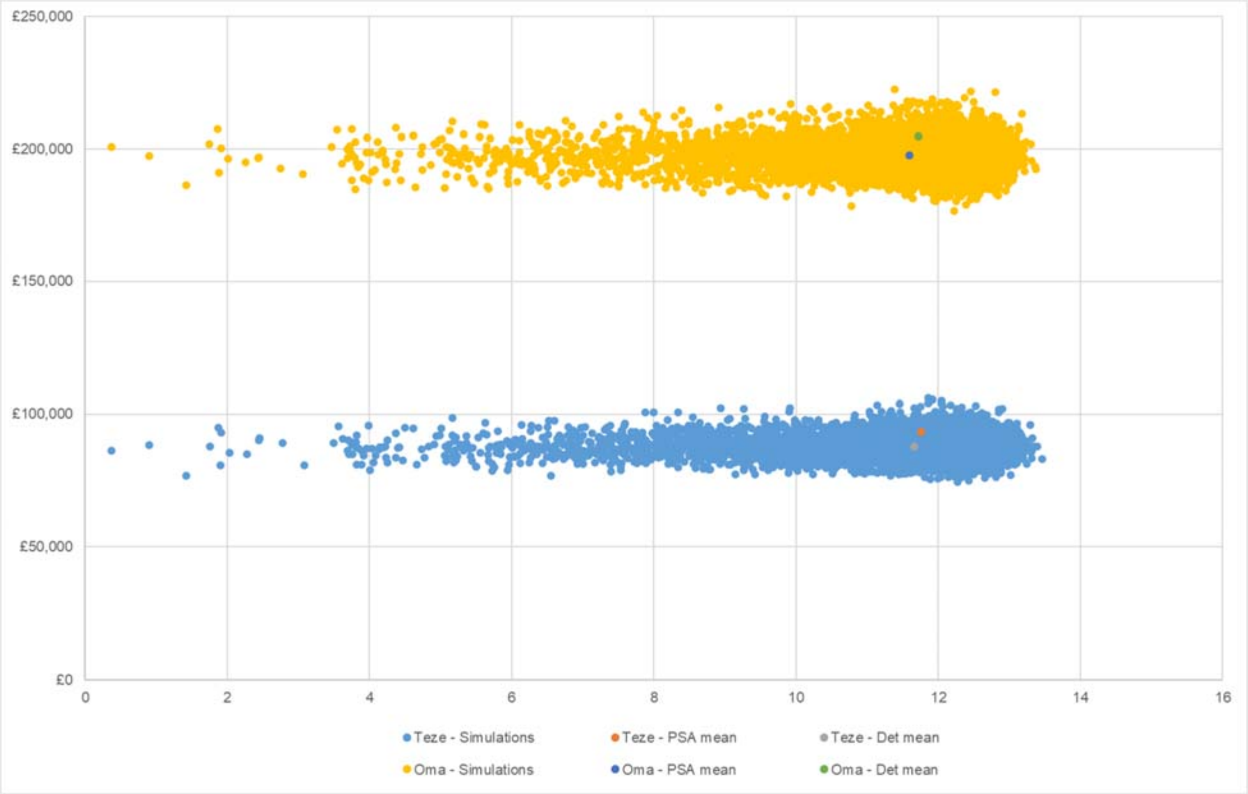
Figure 20: Cost-effectiveness frontier (reslizumab eligible)



Abbreviations: CE, cost-effectiveness.

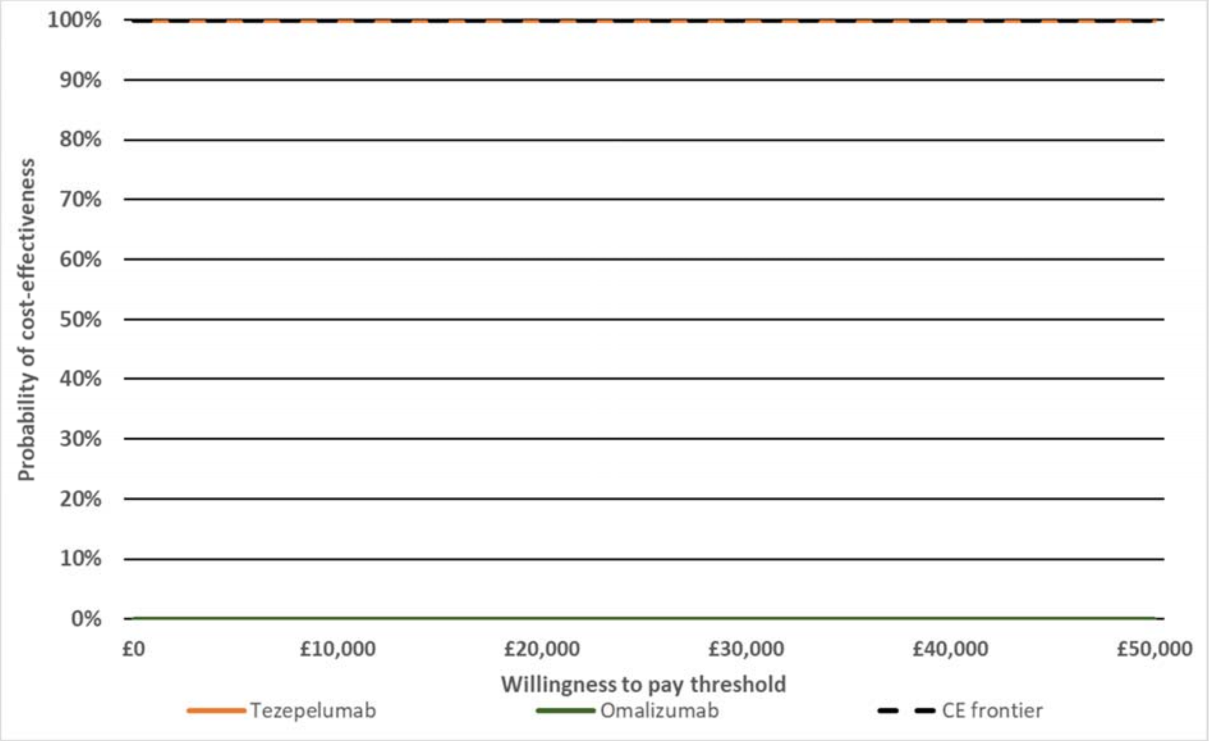
Omalizumab-eligible subgroup

Figure 21: Incremental cost-effectiveness scatter plot (omalizumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

Figure 22: Cost-effectiveness frontier (omalizumab eligible)



Abbreviations: CE, cost-effectiveness.

Technical engagement response form

Tezepelumab for treating severe asthma [ID3910]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise, all information submitted under ‘academic in confidence’ in yellow, and all information submitted under ‘depersonalised data’ in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: ‘academic/commercial in confidence information removed’. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by the end of **20 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Key issues

Key issue	**Does this response contain new evidence, data or analyses?**	**Response**
Exclusion of reslizumab as a comparator	Yes	The company has previously provided an analysis versus reslizumab + standard of care (SoC) in the response to the ERG's Clarification Question B11. For completeness, the deterministic and probabilistic results for that analysis are presented in Table 16 and Table 17 of the present document, inclusive of mepolizumab and benralizumab as comparators, as these biologics are also treatment options in the reslizumab-eligible population.
Definition of treatment response	No	The ERG's proposed alternative definitions for exacerbation response to treatment of ≥20% to ≥50% reduction in exacerbations, yield either little or significant implications for patients' eligibility to continue treatment after one year, when compared with the definition employed in the company's model. For example, relative to the company's definition (any reduction in exacerbations), employing a definition of ≥20% reduction would only change model outcomes and clinical practice for those patients with 6 or more exacerbations in the prior year, who had one less exacerbation in the

		treatment year.* The company expects this would yield very little change vs. using the company's definition. Conversely, a definition of ≥50% reduction has the potential to make many more patients ineligible to continue biologic treatment after 1 year. As examples, a patient with 3 exacerbations in the prior year, who has 2 exacerbations in the treatment year would now be considered an inadequate responder and thus ineligible to continue biologic treatment, as would a patient with 5 exacerbations in the prior year, who has 3 or 4 exacerbations in the treatment year. Thus the company believes this would be a useful topic to discuss with clinical experts at the committee meeting. The company provides commentary in relation to the ERG's post-response assessment transition probabilities scenario later in this response. *Assuming no patients had 11 or more exacerbations in the prior year.
Mismatched subgroups and their provenance in network meta-analyses	Yes	The company's approach, as best as possible, aligns with NICE's recommendations for severe asthma biologics Patient subgroups, defined by blood eosinophil (EOS) count, number of prior annual exacerbations, and allergic asthma diagnosis, were included in the network meta-analyses (NMAs) in order to yield indirect treatment evidence for tezepelumab and its comparators in clinically relevant patient subpopulations. The various NMAs that were subsequently used to inform the economic model were selected since these aligned, or most closely

		aligned, with the NICE-recommended patient populations for each comparator to tezepelumab. The only alternative to using these subgroup NMAs would have been to use the intention-to-treat (ITT) patient population data throughout. But this would have resulted in large proportions of patients being included in analyses who, in clinical practice, are ineligible for biologic treatment based on NICE's recommendations. For the comparison to dupilumab, the EOS <300 cells/μL subgroup NMA captures a higher percentage of the population of interest than the EOS ≥150 cells/μL subgroup NMA and therefore should be retained for use NICE restricts first line (biologic) use of dupilumab to patients with EOS ≥150 cells/μL, who have fractional exhaled nitric oxide of ≥25 parts per billion, had ≥4 exacerbations in the previous year and are not eligible for mepolizumab, reslizumab or benralizumab.[1] Patients who had ≥4 exacerbations in the previous year must have EOS ≥300 cells/μL to be eligible for mepolizumab and benralizumab.[2,3] The reslizumab-eligible population is a subset of the mepolizumab- and benralizumab-eligible populations.[4] Therefore, in the first line biologic setting, the dupilumab-eligible population consists of patients with EOS of 150 to <300 cells/μL.

Table 1 shows patient counts by EOS level from the LIBERTY ASTHMA QUEST, NAVIGATOR and PATHWAY trials. Only data relating to the 200mg and placebo arms of LIBERTY ASTHMA QUEST and the 210mg Q4W and placebo arms of PATHWAY is included, so as to align with the data used in the NMA**.**

Table 1: Patient counts by EOS level

EOS (cells/µL)	LIBERTY ASTHMA QUEST (2018), 200mg and placebo arms[5]	NAVIGATOR [6]	PATHWAY, 210mg Q4W and placebo arms
<150	278	276	[redacted]
150 to <300	257	342	[redacted]
≥300	412	441	[redacted]
Not specified	1	0	[redacted]
Total	948	1,059	275

Abbreviations: EOS, eosinophils

For LIBERTY ASTHMA QUEST, the population of interest (EOS 150 to <300 cells/µL) constitutes a higher percentage of the population with EOS <300 cells/µL (48.0% = 257/[278+257]), than it does of the population with EOS ≥150 cells/µL (38.4%) and therefore the EOS <300 cells/µL subgroup is more representative.[5] The same is true for the NAVIGATOR trial where

		the equivalent values are 55.3% and 43.7% respectively.[6] Similarly for PATHWAY the values are [redacted] % and [redacted] % respectively. Wenzel et al.[7] is also used to inform the comparison to dupilumab in the NMA (EOS <300 cells/μL subgroup), however it does not employ a 150 EOS threshold for stratification and therefore does not provide information in this context. Given patients with EOS of 150 to <300 cells/μL comprise a larger component of the EOS <300 cells/μL subgroup than of the EOS ≥150 cells/μL EOS subgroup in all three trials used in the NMA where this can be determined, the EOS <300 cells/μL EOS subgroup NMA is the more appropriate subgroup to inform the comparison to dupilumab.
Use of Asthma Control Questionnaire (ACQ) cut-off score to define controlled asthma	No	The modelling approach follows precedent from previous NICE appraisals With respect to ACQ cut off, the model structure mirrors that used in three previous NICE appraisals of severe asthma biologics,[1,3,4] whereby an ACQ cut off of 1.5 was used to define asthma control status as either "controlled asthma" or "uncontrolled asthma". "Controlled asthma" is merely the label used for the health state. The model reflects an ACQ cut off of 1.5 The model is structured according to an ACQ cut off of 1.5, meaning that transition probabilities and utilities are derived from trial data for patients with ACQ<1.5 in the case of the "controlled asthma" state. As such the

		term “controlled asthma” is merely a label. The terms “controlled / partially controlled asthma” or “ACQ<1.5” could have been used as alternatives. Recognising that in practice asthma control is not a dichotomous outcome, during the model development phase the company considered the inclusion of a third asthma control health state, “partially controlled asthma”. But owing to the number of subgroups that needed to be considered by the model (stemming from the differing NICE recommended populations for severe asthma biologics) and the need to differentiate between patients taking and not taking maintenance oral corticosteroids, the company anticipated this would lead to some transition probabilities being informed by patient numbers that would become too small. It is for this reason that the company explored the evidence for a biologic specific utility gain, over and above dichotomous asthma control status and exacerbation efficacy (please see response to key issue 9). <u>The model does not overestimate the effectiveness of treatments with respect to the “controlled asthma” health state</u> The ERG’s report states that “*the company’s model classifies patients with partial control as full control, thus overestimating the effectiveness of treatments*.” As stated above transition probabilities and utilities for the “controlled asthma” state have been derived using trial data from patients with

		ACQ<1.5, so it is not correct to say that treatment effectiveness has been overstated. The ERG's ACQ cut off of 1 scenario does not account for the impact on utilities We recognise that the ERG's scenario is exploratory, however reflecting an ACQ cut off of 1, the ERG should have considered the impact on utilities as well as the impact on transition probabilities. In moving from an ACQ cut off of 1.5 to 1, it would be expected that the utility value for the "controlled asthma" heath state would increase, as would the disutility for "uncontrolled asthma". Consideration of transition probabilities alone means that the inputs to the ERG's scenario reflects different ACQ cut offs and therefore the scenario is not internally consistent.
Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'	No	The purpose of including a distinction in the model between exacerbations that occur in patients whose asthma was previously controlled vs. those with asthma previously uncontrolled is to capture differences in health-related quality of life (HRQoL), costs and mortality that arise which would otherwise be indiscernible if this distinction was not made. The approach of differentiating exacerbations on prior control status has also been used in a previous NICE appraisal of a severe asthma biologic.[3] The company does not support the use of a single health state for exacerbation for the reasons outlined above. More specifically:

		• Data from NAVIGATOR and SOURCE that informed the model demonstrates that the proportion of exacerbations resulting in hospitalisation or Accident and Emergency (A&E) visit for patients who were uncontrolled before exacerbation was (generally) higher than for those who were controlled before exacerbation, which leads to differences in HRQoL, costs and mortality which would not be picked up if using a single health state • The existing transition probabilities demonstrate that following exacerbation patients were (generally) more likely to return to the controlled asthma state and less likely to exacerbate again if they were controlled before exacerbation than if they were uncontrolled, which leads to differences in HRQoL and costs – this information would be lost if a single exacerbation state was employed The company acknowledges that its labelling of exacerbation states (“controlled exacerbation”, “uncontrolled exacerbation”) may have led to some confusion and that use of alternative labels “exacerbation, previously controlled” and “exacerbation, previously uncontrolled” would have been more appropriate. Within its report the ERG states that: *“….it seems likely that the transition probabilities from exacerbations to controlled asthma health state are overestimated. This is because patients transitioning from the controlled exacerbation state are more likely to return to the controlled state rather than uncontrolled. However, clinical expert opinion to ERG indicated that:*

		"Baseline stage is either controlled or uncontrolled. In either of those states, patients can exacerbate, but there would be a different risk of exacerbation so your transition probability will be different depending on where you start and after the exacerbation, where patients would go back to probably is dependent on where they came from. If patients were uncontrolled and exacerbating, they are perhaps more likely to go back to being uncontrolled than to being controlled. Whereas if they were controlled and exacerbate they could go back to either being controlled again or to being uncontrolled." Though the company model considers transition from controlled exacerbation state to uncontrolled asthma state, those probabilities are lower than that of the transitions from controlled exacerbation state to controlled asthma state in many instances." The company does not accept that transition probabilities from exacerbations to the controlled asthma health state are overestimated. All transition probabilities were directly informed by patient count data from the NAVIGATOR and SOURCE trials. If following exacerbation in patients who were previously controlled, the probability of returning to the controlled asthma state exceeds that of moving to the uncontrolled asthma state, it is because this is what the trial data showed to be the case. However, the company does accept that it appears illogical to apply a different aggregate utility value to patients who exacerbate according to previous asthma control status and therefore accepts the ERG's pragmatic approach of setting aggregate exacerbation utilities to be equal for those

		previously controlled and uncontrolled. The company has updated its base case accordingly within this document.
Change in transition probabilities at Week 52	No	<u>The modelling approach reflects NICE technology appraisal guidance to stop biologic treatment after one year if the patient has not responded adequately</u> The change in transition probabilities is designed to account for the formal response assessment as specified in NICE technology appraisal guidance for all severe asthma biologics, which is stipulated to occur after one year of biologic treatment for all biologics except omalizumab, for which the assessment timepoint is 16 weeks.[1-4,8] The company expects a response assessment at one year to be included in guidance for tezepelumab and has reflected this in the model via a one-off discontinuation event at 52 weeks, so as to remove inadequate responders from tezepelumab treatment and a change in transition probabilities from week 53 onwards to reflect tezepelumab responder efficacy. The discontinuation percentage and post-response assessment transition probabilities are informed by individual patient data from the tezepelumab trials. <u>The modelling approach follows precedent from previous NICE appraisals</u> The models used to inform all previous NICE appraisals of biologics for severe asthma have employed pre- and post-response assessment transition probabilities, with the change in probabilities being applied from the timepoint at which the response assessment is conducted.[1-4,8]

		Therefore the approach taken in the tezepelumab model is line with that used in previous NICE appraisals of similar products. In the clinical trials, no tezepelumab discontinuations were associated to a lack of response The ERG report states that "*In summary, the model effectively assumes that the effectiveness of tezepelumab and other biologics increases, due to there being fewer non-responders in the pool of patients who continue to take the drug (who transition to SoC). Whilst this is plausible, the ERG is of this opinion that this is likely an overestimate as the model incorporates background discontinuation already. Thus, the transition probabilities prior to Year 1 should already reflect discontinuations. It would have been preferable for the company to model transition probabilities as a function of time, rather than a step function at Week 52.*" With reference to document B of the company submission, Table 27 (NAVIGATOR) and Table 29 (SOURCE) show there were no discontinuations associated to lack of efficacy. Further to this, had inadequate responders already been captured as part of "natural discontinuation" in the model, the calculation for the probability of discontinuation at response assessment in patients without mOCS would have yielded zero values across all subgroups (since both the probabilities for natural discontinuation and discontinuation at response assessment are calculated using individual patient data). For the 3+ Exacs OR mOCS non-

		bio eligible, anti-interleukin five (IL-5) eligible, reslizumab eligible and omalizumab eligible subgroups, the probability of discontinuation at response assessment exceeds the probability of natural discontinuation by a factor of >3. The probability of discontinuation at response assessment was zero for the dupilumab eligible subgroup, most likely as a result of this being the smallest of the subgroups considered by the model (it consisted of only [redacted] patients from the pivotal trials, whereas other subgroups consisted of between [redacted] and [redacted] patients). <u>The company is not aware of means by which post-response assessment transition probabilities could be modelled as a smoother function of time</u> The company agrees with the ERG that in real world clinical practice it is unlikely that all tezepelumab response assessments will be conducted at exactly one year. However the company is not aware of a means by which this could be modelled with improved accuracy and as a smoother function of time as proposed by the ERG. In clinical practice, some response assessments are likely to occur before one year and others later than one year, so applying the change in transition probabilities at one year appears appropriate and aligns with the timing that is expected to be stated in NICE technology appraisal guidance for tezepelumab.

		The ERG's scenario in which post-assessment transition probabilities are assumed to be the same as pre-assessment transition probabilities is unrealistic Aligned to the commentary above, this scenario does not account for the improvement in efficacy for tezepelumab that would stem from the removal of inadequate responders, post response assessment.
Hospitalisation rate for biologics other than tezepelumab may be overestimated	Yes	The ERG identified that in the company base case the simultaneous effects of exacerbations and hospitalisations was incorrect. The company agree that the model was errant in this regard, leading to it overestimating the treatment effect of tezepelumab versus other biologics in terms of exacerbation-related hospitalisations. A revised base case analysis is therefore presented later in this document.
Asthma mortality may have been overestimated	Yes	The ERG's assertion that mortality is overestimated in patients aged <75 years is based on data for a population whose asthma is much less severe than the population of interest for this appraisal The ERG's report states that: "*The ERG is concerned that the probabilities used by the company overestimate asthma-related mortality for the population aged <75 years. As noted in the Health Survey for England (HSE) asthma report 2018: "Almost three-quarters of asthma deaths occur in people aged 75 and over and only one-quarter occur in adults aged 35 to 74 years". However, the asthma mortality for adults aged <75 years has been overestimated in the company's model; for example, in the SoC arm,*

		~37% of deaths occur in the cohort <75 years which is roughly 12% more than the HSE (2018) asthma report estimate as mentioned above. The analysis from the Health Survey for England asthma report captures all asthma-related deaths, that is deaths that occurred in patients of all asthma severities (i.e. across BTS/SIGN guideline steps 1-5). This can be thought as relating to a population with uncontrolled asthma (since death implies uncontrolled). This population is far removed from the population of interest for this appraisal. Not only does this appraisal consider uncontrolled patients only at step 5 (those with severe asthma, in need of high dose ICS and an additional controller), the patients in question also need to belong to the more severe subgroup with 3 or more exacerbations in the prior year or be on maintenance oral corticosteroids. Thus the population of interest has asthma that is significantly more severe than the general population with uncontrolled asthma to which the Health Survey for England asthma report analysis relates. Since the asthma-related mortality rate in the population of interest would be expected to be significantly higher than that relating to the general population with uncontrolled asthma, it follows that the percentage of deaths that occur in patients aged below 75 would also be expected to be higher. The company sought clinical opinion on this point from severe asthma leads who also thought that the percentage of deaths that occur in under 75s would be higher in the population of interest.

		Data from a real-world study which included a cohort of severe uncontrolled asthma patients does not support the ERG's approach of lowering mortality in patients aged below 75 years A recently published retrospective observational study reports all-cause mortality for a cohort with severe uncontrolled asthma, alongside a cohort with (general) asthma and a general population cohort in patients/people who were 12 years or older, using data from a national sample of a French healthcare database (Echantillon Généraliste des Bénéficiaires).[9] A total of 739 patients were identified in the severe uncontrolled asthma cohort. The index year was 2014 and patients were followed for two years. The study reported a 2-year mortality rate and the age distribution of deaths in 10-year age bands. For the cohort with severe uncontrolled asthma, the study found that the percentages of deaths that occurred in patients below the age of 70 and 80 to be 35.6% and 59.3% respectively. From this it is reasonable to assume that the percentage of deaths occurring in those below the age of 75 is approximately 45%. This is higher than the value outputted by the company's model (37%) and significantly higher than the value the ERG is advocating (27%). Further to this, the Roche et al. study[9] considers severe uncontrolled asthma 'all-comers', it is not restricted to the (more severe) population of interest for this appraisal with 3 or more exacerbations in the prior year or on mOCS, for whom the percentage would be expected to be higher still.

		The ERG’s approach to adjusting mortality is not robust The ERG’s report states that: *“…in this appraisal, the ERG performed an ad hoc search for the latest asthma mortality data and located the 2020 asthma mortality data and the number of admission episodes for England (cause of death: J45-J46 Asthma) from the Office of National Statistics (ONS; nomis database).[44]* *Based on the 2020 asthma mortality data which indicated 1,259 asthma deaths out of 83,659 admissions, the average probability of death (annual probability converted to four-weekly) was 0.00116575. The average probability of death (four-weekly) in hospital setting based on company’s asthma mortality estimates used in the model for people aged <65 years was 0.006778, about five times higher than the 2020 asthma mortality data derived from ONS.”* There are limitations with this approach: 1. Population misalignment - The ERG has used asthma-related mortality data collected in patients of all asthma severities (BTS/SIGN guideline steps 1-5) and divided this by the number of asthma hospitalisations, also collected in patients of all asthma severities. As discussed above, this approach is not aligned with the population of interest and considers a population with much less severe asthma. The company believes that, given a hospitalised exacerbation occurs, the associated mortality rate would be higher in patients with severe uncontrolled asthma and ≥3 exacerbations in the prior year or on mOCS, than the mortality rate in (general)

		asthma patients who are hospitalised with an exacerbation. The company sought clinical opinion on this point from severe asthma leads who agreed that the mortality rate would be higher in the population of interest. 2. Inappropriate translation to 4 weekly probability – the ERG's approach yields an initial probability of death for hospitalised exacerbations, based on data for the annual observed number of asthma deaths and asthma hospitalisations in England. The ERG deems this to represent an annual probability and goes on to translate this to a 4-weekly probability for use in the model. However, it is inappropriate to make this translation to a 4-weekly probability because patients in the model only face the risk of asthma-related mortality in the cycle following exacerbation. If patients faced a continuous risk of asthma-related death after hospitalised exacerbation the ERG's approach would be appropriate but this is not the case in the model. As such the ERG's base case accrues hospitalised exacerbation-related deaths at a rate far lower than that stemming from the initial reference data. All-cause mortality in the ERG's base case (and the company's base case) is far lower than the rate in the literature for severe uncontrolled asthma patients Within the Company submission it was demonstrated that all-cause mortality may be underestimated in the company's model versus real world

		mortality in severe asthma patients, based on data from Bourdin et al.[10] The recently published (August 2022) Roche et al. study[9] represents a more appropriate source of information in relation to this appraisal, as it included a cohort of patients whose severe asthma was uncontrolled. The study data collection period of 2014-16 corresponds to a time when there was little availability of biologics for severe asthma, meaning it is appropriate to benchmark mortality in this study to the standard care arm of the cost-effectiveness model (3+ exacs or mOCS, non-bio eligible population), once baseline characteristics have been aligned as best as possible. The cohort of interest from Roche et al. had mean age 62 years and 43% of patients were male, so these values were adopted within the model.[9] Roche et al. found 2-year mortality in the severe uncontrolled asthma cohort to be 8.0%[9]. Table 2 presents the equivalent values using the ERG's and company's base case models, having adjusted baseline characteristics. **Table 2: Mortality in severe uncontrolled asthma patients**

Age	Roche et al[9]	ERG base case	Company base case
2-year mortality	8.0%	1.8%	3.1%

		Thus it is clear that both the ERG's and company's models significantly underestimate real world mortality in severe uncontrolled asthma patients as compared with Roche et al. As mentioned above, the Roche et al. study was not restricted to patients with 3 or more exacerbations in the prior year or on mOCS, for whom the mortality would be expected to be higher still.[9] Thus the company does not accept that mortality in the cohort aged <75 years has been overestimated for the population of interest in the company's model. The company believes it has been underestimated.
Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events	No	It is not correct to use the label "Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events" – the utility gain stems from treatment effectiveness The model structure considers asthma control as a dichotomous variable – patients are either controlled or uncontrolled. This approach represents a very 'blunt instrument' by which to assess asthma control efficacy and is therefore likely to lead to (efficacy) information loss. As described above, the company considered the inclusion a third asthma control health state, "partially controlled asthma" to improve discrimination but owing to the number of subgroups that needed to be considered and the need to differentiate between patients with and without mOCS, the company anticipated this would lead to some transition probabilities being informed by patient numbers that would become too small. It is for this reason that

		the company explored the evidence for a treatment effect on utility over and above dichotomous asthma control status and exacerbations. <u>The evidence to support the utility gain comes from the utility regression analysis conducted on EQ-5D-5L data collected in the tezepelumab clinical trials</u> With respect to the regression co-efficient the ERG report states that: *The ERG notes this is of borderline statistical significance in the company's regression model (p=0.049) and feels that there is no logical justification for this: it is likely a chance finding."* The logical explanation for the treatment effect is that outlined above – the model structure does not discriminate sufficiently with respect to asthma control. The company does not accept that the evidence for a treatment effect on utility is a chance finding - the regression analysis found the coefficient to be statistically significant. The ERG argues that because differences in ACQ, once dichotomous asthma control status has been accounted for, fall below the minimally clinically important difference of 0.5, that the treatment effect on utility is not justified. The company does not agree with this line of argument: It is analysis relating to EQ-5D data that should inform health-related quality of life inputs to the model. Such an approach aligns with the NICE reference case.

		In two previous NICE appraisals of severe asthma biologics, a biologic treatment effect on utility over and above that stemming from the model structure was included In TA565, biologic specific treatment effects on utility were incorporated against asthma control states. Directly observed EQ-5D-5L values from the pivotal trials were mapped to EQ-5D-3L, according to asthma control status and whether patients were taking mOCS or not. In TA278, the day-to-day symptoms health state was differentiated between standard therapy and biologic treatment, with a higher utility applied to the biologic treatment state. In both cases, the biologic treatment effect on utility appears to have been accepted by the committee. Therefore, the approach of applying a biologic treatment effect on utility over and above asthma control status (/day to day symptoms) and exacerbations is in line with that used in previous NICE appraisals of severe asthma biologics.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Additional issues from the ERG report

Issue from the ERG report	**Relevant section(s) and/or page(s)**	**Does this response contain new evidence, data or analyses?**	**Response**
Additional issue 1: Additional data that has been made available since company submission	N/A	Yes	As discussed during the technical engagement call with NICE and the ERG, since the company submission was received, there has been a data release from the DESTINATION study. DESTINATION is the first placebo-controlled long-term safety and efficacy study with a biological therapy in severe asthma. The study demonstrates that over 2 years tezepelumab is well-tolerated, and resulted in sustained improvements in reduction in exacerbations, improved lung function, symptom control and HRQoL. Consistent with results seen in the other

			<u>Phase III clinical trials for tezepelumab, NAVIGATOR & SOURCE</u> DESTINATION is a phase 3, multicentre, randomized, placebo-controlled, double-blind, extension study (NCT03706079) of patients (12–80 years old) who completed NAVIGATOR or SOURCE in which patients were previously randomized to tezepelumab continued treatment.[11] • Patients randomised to tezepelumab 210 mg subcutaneously every 4 weeks were continued on the same treatment. Those previously randomised to placebo were re-randomised 1:1 to tezepelumab 210 mg or placebo subcutaneously every 4 weeks. Resulting in an overall distribution of 3:1 (Tezepelumab:placebo) • Those either continuing on tezepelumab or re-randomised to tezepelumab are referred to as “rand teze” group • Those continuing placebo are referred to as “rand pbo” group • Primary endpoints of exposure-adjusted incidence of adverse events (patients with event/total exposure) (AEs) and serious AEs (SAEs) over 104 weeks

			• Secondary endpoints of AAER over 104 weeks Overall 951 patients were randomised into DESTINATION, with 827 from NAVIGATOR and 124 from SOURCE. The exposure-adjusted incidence of any AEs, any SAEs, and any AE leading to treatment discontinuation in the on-treatment period were lower in the 'rand teze' group than in the 'rand pbo' group across both parent studies (Table 3). • In patients who initially received tezepelumab (n=528) or placebo (n=531) in NAVIGATOR, incidence rates per 100 patient years were 49.62 and 62.66 for AEs and 7.85 and 12.45 for SAEs, respectively, over 104 weeks. • In those who initially received tezepelumab (n=74) or placebo (n=76) in SOURCE, incidence rates were 47.15 and 69.97 for AEs and 13.14 and 17.99 for SAEs, respectively (Table 3) Tezepelumab reduced the AAER over 104 weeks compared with placebo by 58% (rate ratio: 0.42; 95% CI : 0.35-0.51) and 39% rate ratio: 0.61 95% CI: 0.38-0.96 in NAVIGATOR and SOURCE patients respectively.[11]

			Tezepelumab reduced the annualised rate of asthma exacerbations that resulted in hospitalisations or emergency department visit over 104 weeks compared to placebo [redacted] • [redacted] [redacted] [redacted] The absolute incidence of an AE with a fatal outcome during the on-study period in DESTINATION, including the parent studies, was 11 deaths in patients receiving tezepelumab (including one patient who switched from placebo in the parent study to tezepelumab in DESTINATION) and five deaths in those receiving placebo (including one patient who received placebo in the parent study, was randomised to tezepelumab in the LTE and died before receiving their first tezepelumab dose) (Table 4).[11] No patterns were identified in either the causes of the deaths or the relationship of the deaths to the study drug dosing. No deaths were considered to be causally related to tezepelumab by a masked independent adjudication committee.[11] [redacted]

			[redacted]

Table 3: Summary of on-treatment adverse events from DESTINATION

Parent study	NAVIGATOR		SOURCE	
	‘Rand teze’ (n=528)	**‘Rand pbo’ (n=531)**	**‘Rand teze’ (n=74)**	**‘Rand pbo’ (n=76)**
Total time at risk across all patients (years)	917·0	699·0	129·4	100·0
Any AE				
n (%)	455 (86·2)	438 (82·5)	61 (82·4)	70 (92·1)
Incidence (per 100 patient-years)	49·62	62·66	47·15	69·97
Any AE resulting in death				
n (%)	7 (1·3)	1 (0·2)	2 (2·7)	0 (0·0)
Incidence (per 100 patient-years)	0·76	0·14	1·55	0·00
Any SAE				
n (%)	72 (13·6)	87 (16·4)	17 (23·0)	18 (23·7)
Incidence (per 100 patient-years)	7·85	12·45	13·14	17·99

Parent study	NAVIGATOR		SOURCE	
	'Rand teze' (n=528)	**'Rand pbo' (n=531)**	**'Rand teze' (n=74)**	**'Rand pbo' (n=76)**
Any AE leading to discontinuation of treatment				
n (%)	15 (2·8)	21 (4·0)	2 (2·7)	2 (2·6)
Incidence (per 100 patient-years)	1·64	3·00	1·55	2·00
Most common AEs,* n (%)				
Nasopharyngitis	129 (24·4)	123 (23·2)	17 (23·0)	22 (28·9)
Upper respiratory tract infection	71 (13·4)	88 (16·6)	12 (16·2)	8 (10·5)
Headache	56 (10·6)	53 (10·0)	9 (12·2)	10 (13·2)
Asthma	27 (5·1)	61 (11·5)	8 (10·8)	14 (18·4)
Bronchitis bacterial	30 (5·7)	18 (3·4)	8 (10·8)	7 (9·2)

Abbreviations: AE, adverse events; pbo, placebo; SAE, serious adverse events; teze, tezepelumab.

Table 4: Incidence of fatal adverse events during the on-study period by preferred term

[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ‘rand teze’ group included all patients randomised to tezepelumab in the parent study, and the ‘rand pbo’ group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The ‘all teze’ group consisted of patients randomised to tezepelumab in the parent study, plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.
AE=adverse event. LTE=long-term extension. n=number of patients.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case incremental cost-effectiveness ratio (ICER)**
5. Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'	In the base case the model differentiates between exacerbations that occur in patients whose asthma was previously controlled vs. those with asthma previously uncontrolled and used alternative utility assumptions to capture differences in HRQoL	The company accepts that it appears illogical to apply a different aggregate utility value to patients who exacerbate according to previous asthma control status and therefore accepts the ERG's pragmatic approach of setting aggregate exacerbation utilities to be equal for those previously controlled and uncontrolled.	The revised results are presented below. • Anti-IL-5 eligible: Table 5 • Dupilumab eligible: Table 6 • Omalizumab eligible: Table 7 • Non-bio eligible [3+ exacerbations OR mOCS]: Table 8
7. Hospitalisation rate for biologics other than tezepelumab may be overestimated	The rate of exacerbations and hospitalisations in the tezepelumab and SoC arms were drawn from observed count data from the NAVIGATOR and PATHWAY	The company agree that the proposed approach did likely overestimate the treatment effect of tezepelumab versus other biologics in terms of exacerbation related hospitalisations. The	The revised results are presented below. • Anti-IL-5 eligible: Table 9 • Dupilumab eligible: Table 10 • Omalizumab eligible: Table 11 • Reslizumab eligible: Table 16

	studies. These and count data from other studies comparing other biologics are combined in a network meta-analysis, with results reported as rate ratios. The model draws on NAVIGATOR and SOURCE to estimate the probability of an exacerbation, then applies the rate ratios to calculate the probability of an exacerbation with the various other biologic therapies. The ERG identified that in the company base case modelling the effects of exacerbations and hospitalisations simultaneously was incorrect.	revised base case assumes the same split of exacerbations as tezepelumab for other biologics thereby preventing the simultaneous application of multiple relative effects.	Please note that this change impacts all the subgroups except the non-bio eligible subgroup.
Company's base case following technical engagement (or revised base case)			The revised base case results are presented below. • Anti-IL-5 eligible: Table 12 • Dupilumab eligible: Table 13 • Omalizumab eligible: Table 14 • Non-bio eligible [3+ exacerbations OR mOCS]: Table 15Table 8

Amendment - No difference in utilities: Controlled vs. Uncontrolled exacerbations

Table 5: Scenario - No difference in utilities: Controlled vs. Uncontrolled exacerbations (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-2%	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,189,747	-14%	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.

Table 6: Scenario - No difference in utilities: Controlled vs. Uncontrolled exacerbations (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-1%	Dominated

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

Table 7: Scenario - No difference in utilities: Controlled vs. Uncontrolled exacerbations (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-2%	Dominated

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

Table 8: Scenario - No difference in utilities: Controlled vs. Uncontrolled exacerbations (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,680	-1%	£29,680

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

Amendment - Exacerbation split same as TEZ for other biologics

Table 9: Scenario - Exacerbation split same as TEZ for other biologics (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	6%	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£710,119	-32%	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.

Table 10: Scenario - Exacerbation split same as TEZ for other biologics (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	71%	Dominated

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

Table 11: Scenario - Exacerbation split same as TEZ for other biologics (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	12%	Dominated

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

Revised base case:

Table 12: Revised base case (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	4%	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£780,142	-25%	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.

Table 13: Revised base case (dupilumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	67%	Dominated

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

Table 14: Revised base case (omalizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	9%	Dominated

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

Table 15: Revised base case (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER incremental (£/QALY)	% change from original base case ICER	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-			
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,680	-1%	£29,680

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

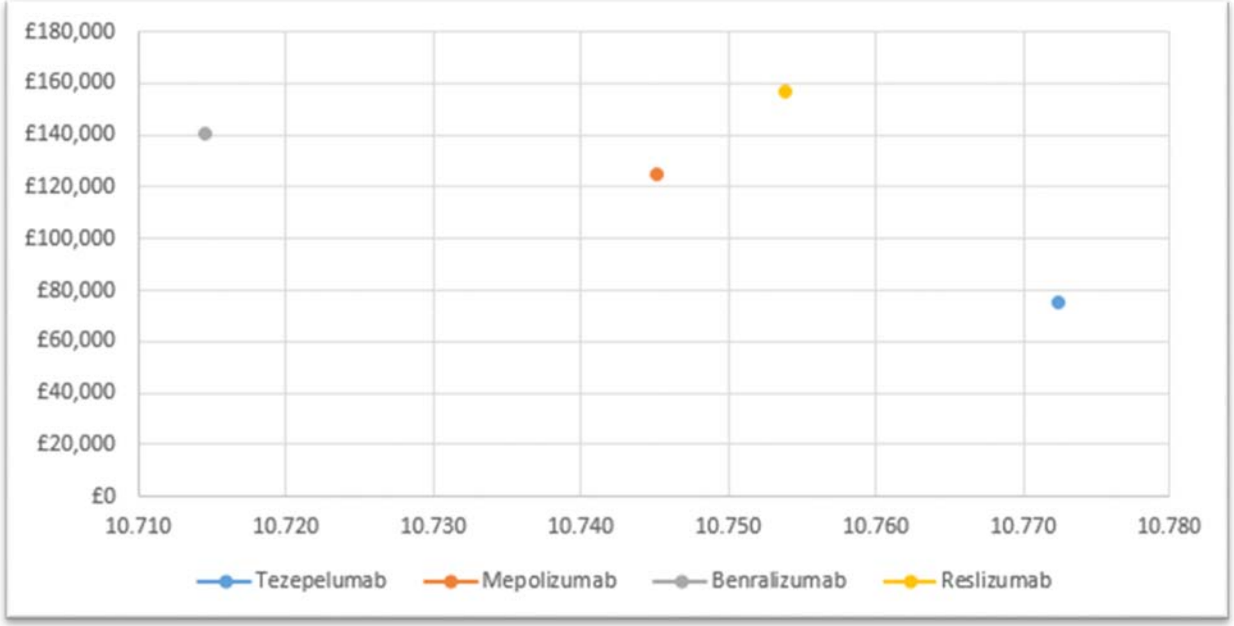
Table 16: Base case results (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALY	Incremental LYG	ICER incremental (£/QALY)	ICER versus Tezepelumab (£/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]	£417,103	Dominated

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

Probabilistic results for reslizumab eligible

Figure 1: Cost-effectiveness plane (reslizumab eligible)



Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs. Results for the comparator biologics were highly congruent with the deterministic results. Consistent with the base case, tezepelumab dominated all of the comparator biologics considered in the reslizumab eligible population. Table 17 presents the probabilistic incremental cost-effectiveness results in detail with the individual simulation scatter plot detailed in Figure 2. Tezepelumab had a 100% probability of being cost-effective at £20,000 and £30,000 per QALY gained. The cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 3.

Table 17: Probabilistic results (reslizumab eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALY	Incremental LYG	ICER incremental (£/QALY)	ICER versus Tezepelumab (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[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]	£208,721	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 2: Cost-effectiveness plane (reslizumab subgroup)

[redacted]

Abbreviations: Benra, Benralizumab; Det, deterministic; ICER, incremental cost-effectiveness ratio; Mepo, Mepolizumab; PSA, probabilistic sensitivity analysis; Resli, Reslizumab, Teze, Tezepelumab

Figure 3: Cost-effectiveness frontier (reslizumab subgroup)

[redacted]

Abbreviations: CE, cost-effectiveness; IL, interleukin.

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Professional organisation submission

Tezepelumab for treating severe asthma [ID3910]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Christopher Corrigan**
2. Name of organisation	**British Society for Allergy & Clinical Immunology (BSACI)**

3. Job title or position	**Emeritus professor of Asthma, Allergy & Respiratory Science, King's College London**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**National Society for health care workers managing patients with inhalant, food and drug allergies and diseases related to allergy including asthma, eczema, urticaria. Funded by subscription.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and	**No**

purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This therapy is one of several recent monoclonal antibodies (also termed "biologicals" or "biologics") developed to for patients with chronic, severe asthma who remain uncontrolled in terms of exacerbations, day to day symptomatology and deterioration in lung function despite maximal "standard of care" therapy which might be defined as treatment with full dosages of inhaled bronchodilator and topical corticosteroid therapy administered with perfect patient compliance and optimal, regularly supervised inhaler technique, additional systemic corticosteroid therapy and minimisation of exposure to other potential provoking factors such as smoke and other pollutants, allergens which may trigger symptoms and relevant occupational agents. The main "aim" of treatment is to reduce or eliminate severe exacerbations of asthma which are potentially fatal and result in severe deterioration of the patient's Quality of Life, and also place considerable demand, both logistical and financial, on both routine and emergency healthcare services. Related aims are to reduce or eliminate chronic, systemic corticosteroid therapy which itself causes wide ranging and unpredictable morbidity, and prevent progressive, irreversible airways obstruction, which likely reflects remodelling of the airways, and which is a feature of the disease in some severe patients.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Existing phase 2 and 3 trials of tezepelumab (summarised for example in: Tezepelumab in the Treatment of Uncontrolled Severe Asthma. Feist J et al. Ann Pharmacother. 2022 May 10:10600280221095540) suggest that treatment is associated with an approximately 66% reduction in the annualised asthma exacerbation rate, which compares favourably with other biological agents and is currently the benchmark of a clinically "significant" response. Reduction or elimination of systemic corticosteroid therapy and arresting of

x cm, or a reduction in disease activity by a certain amount.)	irreversible airways obstruction are other possible benchmarks.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	As stated in section 6 above there is a unmet need for the better management of patients with chronic, severe asthma who remain uncontrolled in terms of exacerbations, day to day symptomatology and deterioration in lung function despite maximal “standard of care” therapy which might be defined as treatment with full dosages of inhaled bronchodilator and topical corticosteroid therapy administered with perfect patient compliance and optimal, regularly supervised inhaler technique, additional systemic corticosteroid therapy and minimisation of exposure to other potential provoking factors such as smoke and other pollutants, allergens which may trigger symptoms and relevant occupational agents. These patients, both adults and children, form a substantial minority of the total and are responsible for most of the activities of severe asthma specialist centres.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Numerous guidelines, both national (e.g. British Thoracic Society, Asthma UK, American Thoracic Society) and international (e.g. European Respiratory Society, Global Initiative for Asthma).
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The pathway of routine management of asthma is well defined and broadly congruent across the world. There is some doubt about the uniform quality of delivery of the management: for example, there is evidence that many patients continue to use inhaler devices sub-optimally (see for example: Is Inhaler Technique Adequately Assessed and Reported in Clinical Trials of Asthma and Chronic Obstructive Pulmonary Disease Therapy? A Systematic Review and Suggested Best Practice Checklist. Dekhuijzen

between professionals across the NHS? (Please state if your experience is from outside England.)	PNR et al. J Allergy Clin Immunol Pract. 2022 Mar 29:S2213-2198(22)00291-4). There is also lack of clarity at present about the precise criteria for eligibility for "biological" (monoclonal antibody) therapy, which in part reflects the fact that the precise potential benefits of these agents are still being defined, as are the precise clinical characteristics of the patients most likely to benefit from any given agent. Typically, patients offered biological therapies will have suffered frequent exacerbations of asthma which take them to hospital despite taking maximal dosages of topical anti-asthma drugs (hopefully with perfect inhaler technique), often with additional oral corticosteroids, which may induce additional morbidity and unwanted effects. Other patients likely to be considered for biological therapies include those with chronically severe symptoms and those with evidence of progressive, irreversible airways obstruction which likely reflects airways remodelling.
• What impact would the technology have on the current pathway of care?	It will form another type of "biological" therapy for severe asthmatic patients as described above. In contrast to existing biological agents, which target IgE receptor binding or Th2-type cytokines, tezepelumab targets thymic stromal lymphopoietin (TSLP) which, along with IL-33 and IL-25 comprise the "alarmin" cytokines released by airways epithelial cells damaged by environmental insults such as particulates, proteases, allergens and exposure to respiratory tract viruses and bacteria in susceptible individuals. These alarmins act on local, type 2 innate lymphoid cells (ILC2s) to release large quantities of Th2-type cytokines, which in turn differentiate local T-cells into Th2-type cells, which further contribute to Th2-type cytokine production but critically are potentially susceptible to inhibition by corticosteroids, whereas ILC2s are not (for a more detailed discussion see: Calcilytics: a non-steroidal replacement for inhaled steroid and SABA/LABA therapy of human asthma? Corrigan CJ. Expert Rev Respir Med. 2020 Aug;14(8):807-816. doi: 10.1080/17476348.2020.1756779). Thus, in asthmatic patients whose disease is relatively resistant to corticosteroid therapy, it may be hypothesised that ILC2s make a substantial contribution to local Th2-type cytokine secretion, which is in turn responsible for the eosinophilic airways inflammation characteristic of "eosinophilic" asthma, and that inhibition of alarmins such as TSLP will exert greater benefit in the disease than targeting Th2-type cytokines such as IL-5 or its receptor alone. In addition, TSLP also promotes the differentiation of Th0 cells into Th17 cells via IL-1β, TGF-β, and IL-6. Th17 cells act on airway epithelial cells, induce neutrophilic airway inflammation, and play a central role in the pathogenesis of non-type 2, "neutrophilic" asthma, consistent with the hypothesis that TSLP is a candidate therapeutic target not only in type 2, "eosinophilic" asthma, but also in non-type 2, "neutrophilic" asthma (for further details see: Ando K et al. Comparative efficacy and safety of Tezepelumab and other biologics in patients with inadequately

	controlled asthma according to thresholds of Type 2 inflammatory biomarkers: A systematic review and network meta-analysis. Cells 2022 Mar; 11(5): 819; doi: 10.3390/cells11050819). This is consistent with studies suggesting that therapy with tezepelumab reduces exacerbations, improves lung function and reduces type 2 biomarkers compared with placebo control in patients with severe, uncontrolled asthma with or without perennial allergy (the latter patients would not qualify as suitable for therapy with the anti-IgE biological agent omalizumab: see Corren J et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma and perennial allergy. J Allergy Clin Immunol Pract. 2021 Dec;9(12):4334-4342.e6. doi: 10.1016/j.jaip.2021.07.045). Similar findings were seen in the NAVIGATOR study (Menzies-Gow A et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021 May 13;384(19):1800-1809. doi: 10.1056/NEJMoa2034975) in which 4 weekly therapy with tezepelumab administered for a total of 52 weeks reduced exacerbations and improved lung function compared with placebo in a group of 1061 patients aged 12-80 yr regardless of their blood eosinophil counts. These studies did not demonstrate a systemic corticosteroid sparing effects of the therapy, nor a minimally clinically significant improvement in day to day symptom scores. Finally, alarmins such as TSLP have been implicated in causing remodelling changes in the airways (see for example An G et al. Combined blockade of IL-25, IL-33 and TSLP mediates amplified inhibition of airway inflammation and remodelling in a murine model of asthma. Respirology. 2020 Jun;25(6):603-612. doi:0.1111/resp.13711), raising the possibility that anti-alarmins such as tezepelumab may inhibit irreversible airways obstruction caused by remodelling (although they are unlikely to reverse established changes, and in an ideal world they would be given prophylactically to patients identified in advance as being susceptible to such remodelling: at present this is not possible).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ	Tezepelumab is administered subcutaneously by injection typically 4 weekly in line with most other biological therapies for asthma, so apart from the intrinsic cost of the medication and the additional person hours required to administer it, it should not require any significant change in healthcare resource usage,

between the technology and current care?	given that the treatment is likely to be administered, as with all biological agents, in existing, tertiary specialist asthma centres across the country.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist asthma centres as above.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As above, existing facilities should be adequate to deliver the technology, with a brief period of training common to all personnel concerned with the treatment of severe asthmatic patients with biological agents. Again, in common with existing biological agents it seems very unlikely that the treatment will be associated with any significant unwanted effects, at least in the short term.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	See comments in section 9 above. There is very little tangible evidence at present that the treatment will prolong life compared with other biological therapies, but this is conceivable if, for example, it inhibits irreversible airways obstruction in severe asthmatic patients.
• Do you expect the technology to increase health-related quality of	Possible, if the treatment can be directed to patients likely to benefit specifically from anti-alarmin therapy as discussed above.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	See comments above.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	See comments above. The technology is no more difficult to administer than existing biological therapies, the administration of which is routine in asthma specialist centres. Although tezepelumab is a relatively new drug, and there are at present few studies or an accumulation of clinical experience that might reveal long term unwanted effects of this or indeed any other biological therapy for asthma, there is no reason at present to suppose that the technology will not be widely tolerated, with insignificant immediate, unwanted effects.

tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As mentioned above, the precise indications for the commencement of biological therapies such as tezepelumab are not clearly and universally defined outside the broad criteria outlined in section 9. Currently the criteria by which it is possible to predict the response of any patient to any of the current range of biological agents are still being defined, as is the “optimal” duration of therapy. While it is possible that additional tests will be uncovered in the future as useful, at present these tests are framed around the “routine” testing (lung function, blood leukocyte counts, induced sputum, FeNO, urinary metabolites) to which all severe asthmatics are currently subject.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not in general, although if, as is possible, prolonged use of anti-alarmin biological agents results in deceleration of progressive, irreversible airways obstruction in chronic, sever asthmatic patients I am not clear as to how far this might be reflected in QALY assessments.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, in the senses already referred to above, that anti-alarmin biologicals may be effective for treatment of all “types” of airways inflammation in patients with asthma, by-passing corticosteroid resistance and possibly altering the natural history of airways remodelling and long term obstruction. As with all novel

impact on health-related benefits and how might it improve the way that current need is met?	therapies, however, the “size” of this potential is difficult to predict.
- Is the technology a ‘step-change’ in the management of the condition?	No, but a potentially significant advance.
- Does the use of the technology address any particular unmet need of the patient population?	See comments above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient’s quality of life?	Biological therapies for asthma therapy have so far been uniformly relatively free of unwanted effects, at least in the term of treatment, so fortunately this is unlikely to be an issue (but should still be subject to continuous scrutiny).
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK	Yes

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Most would agree that the most significant outcomes for severe asthmatic patients are fewer or no severe exacerbations, requiring no unplanned visits to hospital, minimisation or elimination of systemic corticosteroid therapy an improvement in lung function, with concomitant improvement in Quality of Life. These are the things that are already measured in trials, although by definition they provide relatively little evidence of the sustainability of such outcomes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge, although the time scale of observation for such possible adverse effects is still relatively very short.
19. Are you aware of any relevant evidence that might not be found by a systematic	Only the emerging evidence for the possible effects of inhibiting the remodelling, as well as the pro-inflammatory effects of the alarmin cytokines: any clinical effects of this are unlikely to be apparent in

review of the trial evidence?	“conventional” clinical trials of short duration.
20. Are you aware of any new evidence for the comparator treatment(s) for relevant NICE technology appraisal guidance?	None that cannot be revealed using a literature search “tezepelumab asthma”.
21. How do data on real-world experience compare with the trial data?	Generally favourably.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not from the point of view of the assessors. Some analyses (for example, see: Rind DM et al. The effectiveness and value of tezepelumab for severe asthma: A summary from the Institute for Clinical and Economic Review’s California Technology Assessment Forum. J Manag Care Spec Pharm, 2022 May;28(5):577-580) have commented that black patients are under-represented in the current clinical trials of tezepelumab, although black people more commonly suffer from asthma than white, particularly in the United States.
22b. Consider whether these issues are different from issues	

with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Tezepelumab is the first anti-alarmin biological available for the treatment of chronic, refractory asthma • As an anti-alarmin therapy it may be suitable for a wide spectrum of severe asthma patients with both eosinophilic and neutrophilic airways inflammation, obviating the need to develop practical methods of distinguishing these in the clinic • It remains to be demonstrated convincingly that tezepelumab therapy is corticosteroid sparing or reduces day to day asthma symptoms to a minimally clinically significant extent, although it clearly reduces the frequency of disease exacerbations substantially • Anti-alarmin therapy may also alter the natural history of airways remodelling which may lead to irreversible airways obstruction, although it would be better given prophylactically in this regard to patients identified (in the future!) as at particular risk • The coast per QaLY is likely to be at least comparable with, and perhaps better than existing biological agents

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……………………………………………………………………………………………

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Patient organisation submission

Tezepelumab for treating severe asthma [ID3910]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Asthma + Lung UK (A+LUK)
3. Job title or position	Health Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Asthma + Lung UK believe that every breath matters - and that the right to breathe freely applies to everybody, regardless of income, age, ethnicity, gender, or background. Even before Covid-19, NHS hospital admissions for lung conditions were rising three times faster than average admissions, and lung disease is now the third most common cause of death in the UK. Asthma and Lung UK aim to reduce this by 20% by 2027 with four key goals: • Prevent lung disease wherever they can • Diagnose lung disease earlier and more accurately • Enable everyone to live well with a lung condition • Drive life-changing research and innovation Asthma + Lung UK is proud to be registered with the Fundraising Regulator, the independent regulator of charitable fundraising. Our organisation receives funding from a variety of supporters, including but not limited to: - trusts and foundations - corporate partners - major donors - pharmaceutical companies - https://www.blf.org.uk/our-work-with-the-pharmaceutical-industry - legacy and wills - community and events fundraising

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	We have not entered into any sponsorship agreements with AstraZeneca, however we have received grant donations from them for our policy and health advice projects. AstraZeneca grant donations during past 12 months: - £50,000 funding toward Taskforce for Lung Health's Year 5 (2022) activities, focused on achieving all objectives that were set out in the 5-year plan. In 2022, this included implementing a public facing campaign to increase awareness of lung health and continuing to develop the Lung Health Data Tracker, which has a vital role to play in the future of lung health influencing and policy change work that will be needed to continue to improve outcomes, quality of life and treatment options for people living with a lung condition. - £25,000 funding towards ALUK's digital COPD patient passport project, to help give people living with COPD the knowledge, skills and self-confidence to better manage their condition. The passport asks a series of questions to check if people living with COPD have the right information about the care they are entitled to. The passport then generates apersonalised COPD report which equips users with the information and resources they need to access support, have constructive discussions with their healthcare professionals and ultimately to better manage their condition.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We have no links to the tobacco industry and our internal guidelines would prevent this.
5. How did you gather information about the experiences of patients and	Information about the experiences of patients and carers living with asthma is gathered regularly through our helpline, email and social media interactions with people with asthma. Asthma UK also conducts patient surveys, focus groups and qualitative interviews.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment for the condition. On average, 4 people die from an asthma attack in the UK every day[1] and more than 1400 people died from an asthma attack in England and Wales in 2018 [2]. Severe asthma affects around 3.6% of people with asthma – which equates to around 173,000 people in England and Wales.[3] The National Review of Asthma Deaths highlighted that almost 40% of asthma deaths were patients who had severe asthma.[4] Severe asthma does not respond well to standard treatments and requires more intensive therapies with significant side effects to control symptoms and prevent asthma attacks, hospitalisations and deaths. People with severe asthma fall outside the robust evidence-base that informs most asthma care, requiring specialist treatment and pathways. Until the recent NICE COVID-19 rapid severe asthma guideline, there had been no dedicated NICE guideline for treating severe asthma. Ongoing severe symptoms and a complex medicines regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions can lead to further social isolation and economic disadvantage, as well as high costs for the NHS.[5] As such, people with

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[1] Data via Office of National Statistics (ONS; England and Wales), National Records of Scotland, Northern Ireland Statistics and Research Agency (NISRA). Data for asthma deaths 2011–2020 used.

[2] Office for National Statistics, Deaths Registered in England and Wales 2018. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2018, (July 2019).

[3] Hekking P, et al, 'The prevalence of severe refractory asthma', The Journal of Allergy and Clinical Immunology, 135(4), (2015)

[4] Royal College of Physicians, 2014, 'Why asthma still kills: the National Review of Asthma Deaths (NRAD)', accessed at https://www.rcplondon.ac.uk/file/868/download?token=JQzyNWUs

[5] D'Amato, Gennaro, et al., "Treating severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab): a review." *Multidisciplinary respiratory medicine* 9.1 (2014): 23.

uncontrolled severe asthma cost four times as much to treat as the average patient.[6] What is more, people with severe asthma remain symptomatic on high doses of treatment. However, a lack of referrals to a specialist for an assessment often leads to patients being left on continuous courses of oral steroids.[7] Oral steroids are known to cause toxic or debilitating side effects including mood-swings, anxiety, increased appetite, diabetes, cataracts and osteoporosis.

Experiences of people living with severe asthma

Our report 'Falling into isolation: Lived experience of people with severe asthma'[8] highlights through qualitative interviews the experiences of six adults with severe asthma. The interviews reiterated that living with severe asthma is so much more than asthma attacks and occasional hospital admissions. It can have devastating consequences on every aspect of people's lives. They may feel isolated, lonely and scared, left without hope or the right support. For example:

"But, obviously, 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." (Participant 2)

"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)

"*They were just saying to my husband well, we've tried everything and she's not responding. And all I could remember was the clock on the wall and I was just staring at the clock, thinking that when am I going to stop breathing because it's getting too painful, I just can't carry on anymore. And that experience, I think, is still stuck with me every time I can't breathe. It just brings all that back to me. And I think that's part of my panic and I just start breathing, getting anxiety."* (Participant 1)

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[6] Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', Thorax (2017), https://doi.org/10.1136/thoraxjnl-2017-210531

[7] Asthma UK, 'Slipping through the net: The reality facing patients with difficult and severe asthma', (2018), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk-severe-asthma-gh-final.pdf p.8

[8] Lottie Renwick, Asthma UK, 'Falling into isolation: Lived experience of people with severe asthma' (2020) https://www.asthma.org.uk/support-us/campaigns/publications/falling-into-isolation/

	We also found that severe asthma can have a huge impact on work or school. For example: *"Yes, and the worst thing was trying to get used to it, from being such an active person and working fulltime, it was just trying to get used to it because I just couldn't work. For quite a long time, I just couldn't work"* (Participant 1) *"I've been off work, most of the time this year because of my asthma. I've literally had no life, really. And then when I was in Year 11, my school attendance was 43%."* (Participant 5) "*And then I knew it was serious when I retired from my job at the age of 30, because I was spending more time as a patient than I was as a nurse."* (Participant 6) Previous research Asthma UK has conducted found that even across the far broader asthma population, 20% of people aged 0-59 miss 1-4 days of work or education a year due to their asthma, whilst 19% miss 10 or more days.[9] We also know from these interviews severe asthma can create a huge burden on family members and carers. For example: *"I think it was a big relief [the severe asthma diagnosis] for my parents as well, because I think they felt the burden as well. Because they had to stop work to look after me. So, obviously, they had the financial burden. I think that they felt that they were labelled as well, because I was still poorly despite them helping me administer my medication and things. Even though it was asthma, it was a separate asthma condition*" (Participant 2).

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[9] Asthma UK, 'Annual Asthma Survey 2016 report', 2017, p.31, Accessed at: https://www.asthma.org.uk/share/?rid=6770

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Oral corticosteroids (OCS) The existing treatments for severe asthma are extremely limited. Patients predominantly rely on OCS to control their symptoms, which can cause toxic and debilitating side effects, particularly when taken for long periods, which in cases of severe asthma, they often are. A survey into the side effects of OCS used by people with asthma was conducted by Asthma UK in 2017. Various side effects were reported, including 56% reporting weight gain; 37% felt more anxious and 33% reported aching and cramping muscles and joints.[10] NHS England reports that the side-effects of maintenance OCS, which "will affect the majority of patients with severe asthma" include diabetes, hypertension, cataracts, osteoporosis, glaucoma, skin disease, reflux oesophagitis, non-alcoholic fatty liver disease and obesity.[11] Likewise, a study by Sweeney et al. which presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry), showed that OCS use results in a higher prevalence of comorbidities, including type II diabetes, hypertension and osteoporosis.[12] . It has been shown that *four or more* courses in a year is associated with significantly greater odds of a person developing osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts[13]. In fact, one study has shown that cumulative exposures, equivalent to just four courses of oral steroids over a lifetime, are associated with adverse outcomes.[14]

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[10] Broadbent C, Pfeffer P, Steed L, Walker S, 'Patient-reported side effects of oral corticosteroids', (2018) European Respiratory Journal 2018 52: PA3144

[11] NHS England, Specialised Respiratory Services (adult) – Severe Asthma, Service Specification: 170002/S. Accessed at: https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf, July 2019.

[12] Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. 'Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry'. Thorax 2016; 71:339-346 https://thorax.bmj.com/content/71/4/339

[13] https://www.ncbi.nlm.nih.gov/pubmed/28456623

[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6121746/

	Lehanne's life has been devastated by her severe asthma. *"Being on high doses of corticosteroids for such a long time has led to all sorts of health problems from their side effects including bone damage. I've had a hip replacement and surgery on my neck because my bones have weakened and I also live in constant pain from problems with my lower back. I am on regular nebulisers and cannot leave the house without my portable nebuliser. Daily, I take home infusions of Bricanyl and every five weeks I'm admitted to the Royal Brompton hospital for ten days treatment of intravenous infusion of aminophylline, hydrocortisone and physiotherapy*."[15] Sadly, Lehanne, like many people with severe asthma, did not qualify for the biologics available at the time. She reflected:, *"life is an endless stream of good periods interspersed with episodes of deterioration which end with me being admitted to hospital. I spent last Christmas in hospital being intubated because I couldn't breathe. My husband is very understanding and does his best to help, but it's stressful and difficult for both of us. I'm desperate for new treatments as are so many of us who live with severe asthma. I really hope the new drugs becoming available will make a difference to our lives."* [16] Biologic treatment The introduction of biologics to treat asthma has proved to be life-transforming for people with severe asthma who are eligible for them. For example, Jane, who was diagnosed with severe eosinophilic asthma and started taking mepolizumab (another biologic treatment for severe asthma) said, *"Two weeks after my first injection I could climb hills in the Peak District. After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I'm actually thinking about increasing the number of hours I do. This treatment has really transformed my life."*

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[15] Asthma UK, 'Press release: New generation asthma drug gets approval for NHS use', accessed at: https://www.asthma.org.uk/about/media/news/new-generation-asthma-drug-gets-approval-for-nhs-use/, (2017)

[16] Ibid

	Jenny was diagnosed with severe asthma and treated with a biologic after suffering from a sudden severe asthma attack whilst on holiday and ended up in hospital for 10 days. *"Since having monthly Xolair injections to reduce my allergic response, at least I'm able to go outside in summer now."*[17] Our forthcoming qualitative report also highlighted the impact biologic treatment can have[18]. For example: *"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) *"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) In effect, except for biologic treatment, therapeutic options are limited for patients with severe asthma whose symptoms cannot be controlled with inhaled steroids and they often must rely on toxic oral steroids.
8. Is there an unmet need for patients with this condition?	The introduction of biologics for treating the condition has truly transformed the lives of many with severe asthma, but thousands may not be eligible for current treatments and even those that are eligible, may not respond to them. Therefore, we urgently need more biologic treatment options for those who have not responded to the biologics they are currently eligible for, as well as those not eligible for any biologic treatment at all. Our report, 'Living in Limbo', highlighted that only around 60,000 people with severe asthma are eligible for existing biologic treatments. This means around 140,000 people with severe

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[17] Asthma UK, 'How I cope with severe asthma', accessed at: https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/how-i-cope-with-severe-asthma/

[18] Lottie Renwick, Asthma UK, 'Falling into isolation: Lived experience of people with severe asthma' (2020) Not yet published

	asthma are not yet eligible for any biologic treatment. Furthermore, our report found that 4/5 of those eligible currently are not receiving biologic treatment. [19] Tezepelumab is the first biologic to reduce all clinical biomarkers (FeNO, Blood eosinophils & IgE), and the phase II & III data demonstrated improvement in patient outcomes in a broad population of severe asthma patients regardless of clinical biomarker levels. This is of great importance given that many patients with uncontrolled asthma have multiple drivers of inflammation and multiplied elevated biomarkers.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Biologic treatment has transformed the lives of many with severe asthma. They offer people with severe asthma the opportunity to control their symptoms and live a life unhindered by their condition. As well as the reduction in symptoms, asthma attacks and hospital admissions, people with severe asthma are given a better quality of life with biologic treatment. As highlighted in the quotes above, they can do more, work, socialise and exercise, which they may not have been able to do before. This can also greatly alleviate pressure on family members and carers.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	NA

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[19] Asthma UK, 'Living in Limbo: the unmet need in difficult and severe asthma', Accessed at: https://www.asthma.org.uk/support-us/campaigns/publications/hidden-harm/living-in-limbo/

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our report, ‘The Great Asthma Divide: Annual Asthma Survey 2019’ has shown that those on lower incomes are more likely to have uncontrolled asthma and experience more asthma attacks.[20] Therefore, they may be more adversely impacted by severe asthma. Women are more likely to have asthma, have more severe symptoms, and are more likely to die from their asthma.[21] We believe that Tezepelumab has the potential to drive much needed improvements in mortality within this group.

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[20] Andrew Cumella, Asthma UK, The Great Asthma Divide: Annual Asthma Survey 2019, (2020) Accessed at: https://www.asthma.org.uk/58a0ecb9/globalassets/campaigns/publications/The-Great-Asthma-Divide.pdf

[21] https://www.asthma.org.uk/support-us/campaigns/publications/asthma-women-report/

Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Severe asthma is so much more than asthma attacks and hospital admissions. It can have devastating consequences on every aspect of people's lives. They may feel isolated, lonely and scared, left without hope or the right support.
- There is a substantial unmet need for people with severe asthma in the treatment options available to them. They may have to rely largely on high doses of OCS to control their symptoms, which can have toxic side effects such as osteoporosis and diabetes.[22]
- The introduction of biologics for treating the condition has truly transformed the lives of many with severe asthma, but thousands may not be eligible for current treatments and even those that are eligible, may not respond to them.
- With Tezepelumab demonstrating improvements in patient outcomes in a broad population of severe asthma patients regardless of clinical biomarker levels, it shows strong signs of making a huge difference to this vulnerable group of patients.

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[22] Asthma UK, https://www.asthma.org.uk/advice/inhalers-medicines-treatments/steroids/ (accessed 12/02/2019)

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TEZEPELUMAB FOR TREATING SEVERE ASTHMA [ID3910]

A Single Technology Appraisal

EAG Review of Company's Response to Technical Engagement

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

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1. INTRODUCTION

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to the technical engagement (TE) report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of tezepelumab (ID3910). Each of the issues outlined in the technical report are discussed in further detail in Section **Error! Reference source not found.**.

In response to TE, the company updated their base case and presented some additional clinical data from a new trial. However, these data were not incorporated into the analyses. Nevertheless, the EAG has reviewed the additional evidence presented by the company.

A response to each of the key issues has been presented in the sections below and structured as follows:

- Section **Error! Reference source not found.**: EAG response to the company's submission at technical engagement
- Section **Error! Reference source not found.**: EAG response to updates in the company's base case
- Section **Error! Reference source not found.**: EAG response to additional evidence provided by the company
- Section 5: EAG response to stakeholder comments received during technical engagement.

In addition, this response is accompanied by an appendix containing the results of the economic model (with EAG scenarios) after confidential patient access scheme (cPAS) discounts have been applied for comparators to tezepelumab.

Please note that the results in this document therefore only contain the PAS discount agreed for tezepelumab.

2. EAG RESPONSE TO COMPANY'S SUBMISSION AT TECHNICAL ENGAGEMENT

This section contains the EAG's response to the company's submission at TE.

2.1. Key issue 1: Exclusion of reslizumab as a comparator

During TE, EAG raised the fact that other anti-IL5 biologics could also be relevant comparators in the reslizumab eligible population. Following this, the company has now included as part of their TE response the deterministic and probabilistic results for reslizumab eligible population incorporating mepolizumab and benralizumab as relevant comparators. See Section 3.1 for the updated results.

2.2. Key issue 2: Definition of treatment response

The EAG is of the opinion that the definition of treatment response is unlikely to be an issue exclusively for tezepelumab as other biologics also deal with severe asthma patients with higher number of exacerbations. Both clinical expert opinion to EAG and the stakeholder response by British Thoracic Society (BTS) to technical engagement have clearly indicated that 'any reduction in exacerbations or mOCS dose from baseline' cannot be a robust definition of response. However, the appropriate definition to be used is subject to discussion with the clinical experts.

The company has indicated in their TE response, and the EAG agrees, that it would be to elicit views from clinical experts and resolve the uncertainty associated with the definition of treatment response as this will have implications for the patient numbers post-response and in turn on the post-response transition probabilities. This also relates to the issue detailed in Section 2.6.

2.3. Key issue 3: Mismatched subgroups and their provenance in network meta-analyses

In their response to TE, the company asserts that the correct subgroup NMA to use for comparisons with dupilumab is the EOS <300 cells/μL subgroup NMA. This is because the company notes patients with the relevant EOS count (150-300 cells/μL) formed a greater proportion of the population in this NMA than in the EAG's preferred NMA, which included patients with EOS ≥150 cells/μL. However, the EAG regards that the make-up of populations by

EOS count is less important than the expected similarity between the treatment response in the entire NMA subgroup and the treatment response in the subgroup relevant for this specific comparison (i.e., EOS count 150-300 cells/µL). The company have not made a representation in this regard; and the EAG's clinical advice remains that the NMA for subgroup of patients with EOS ≥150 cells/µL is most appropriate for use in the comparison with dupilumab.

2.4. Key issue 4: Use of Asthma Control Questionnaire (ACQ) cut-off score to define controlled asthma

Though the EAG agree with the company that using the ACQ cut off of 1.5 is in line with the previous NICE appraisals in asthma, the EAG would like to draw to attention that as per the latest NICE health technology evaluations manual, a statement that assumptions related to the model structure or health states have previously been accepted in prior submissions to NICE is insufficient; rather, these should be justified every time for each new decision problem[1]. The EAG notes that Juniper et al.[2] states: "For all three versions of the ACQ, the crossover point between well-controlled and not well-controlled is close to 1.00. This means that below 1.00 patients are more likely to have well-controlled asthma and above 1.00 they are more likely to have not well-controlled asthma". Therefore, EAG maintains its opinion that classifying patients as "controlled" based on an ACQ cut-off of 1 would be more appropriate.

Table 1 and Table 2 below illustrate the difference between company's and EAG's preference regarding ACQ cut-off.

- At a cut-off of 1.5, 38 of every 100 patients classified as 'well controlled' will in fact be not well controlled.
- At a cut-off of 1.0, only 28 patients will be misclassified as controlled when they are not well controlled.

The higher cut-off therefore overestimates the numbers of patients defined as well controlled, thus exaggerating the effectiveness of treatment. The EAG notes that the complementary effect is observed in terms of patients who are defined as not well controlled but are actually well controlled: the 1.5 cut-off overestimates the numbers uncontrolled.

The opinion of the EAG is that from a decision maker's perspective faced with the opportunity cost of treatment, it is more important to be certain as to whether a patient has controlled asthma (i.e., has responded to treatment) than whether or not they have failed to respond, and not to overestimate the effectiveness of the treatment. Please note that the EAG scenario used the PPV earlier and realised it needs to be corrected using the correct NPV corresponding to the ACQ cut-off of 1 (i.e., 0.72). See Section 3.2 for updated results.

Further, regarding the EAG scenario using the ACQ cut-off of 1, EAG considers company's observation about the impact on utilities plausible however EAG does not have the access to the necessary EQ-5D data to modify the utilities based on the proposed ACQ cut-off.

Table 1: Company's preference regarding ACQ cut-off

	ACQ cut off of 1.5 (company's preference)		
	Well controlled	Not well controlled	Total
Positive predictive value (PPV)* = 0.87 (diagnosed not well controlled)	13	87	100
Negative predictive value (NPV)** = 0.62 (diagnosed well controlled)	62	38	

*If a patient has an ACQ score of 1.5 or greater, there is an 87% chance that their asthma is not well controlled.

**If a patient has an ACQ score of less than 1.5, there is a 62% chance that their asthma is well controlled.

Table 2: EAG's preference regarding ACQ cut-off

	ACQ cut off of 1 (EAG's preference)		
	Well controlled	Not well controlled	Total
Positive predictive value (PPV)* = 0.83 (diagnosed not well controlled)	17	83	100
Negative predictive value (NPV)** = 0.72 (diagnosed well controlled)	72	28	

*If a patient has an ACQ score of 1 or greater, there is an 83% chance that their asthma is not well controlled.

**If a patient has an ACQ score of less than 1, there is a 72% chance that their asthma is well controlled

2.5. Key issue 5: Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'

As mentioned in the EAG original report, clinical opinion to EAG indicated that if patients were controlled and exacerbating, they could go back to either being controlled again or being uncontrolled. Stakeholder response from BTS also indicated that clinically, an exacerbation is not differentiated as controlled or uncontrolled. TA 565[3] committee papers (p142 of the EAG report) also mentioned that there was discrepancy between the model diagram in company's report versus the model and resulted in difficulty interpreting the model structure. Therefore, the EAG is unconvinced by the company's claim based on the trial-derived transition probabilities that, following exacerbation, patients were more likely to return to the controlled asthma state if they were controlled before exacerbation than if they were uncontrolled.

Further, the EAG notes that the incorporation of the equal utility assumption for the two exacerbation states based on prior control status in the revised company base case has partially addressed this issue although the uncertainty associated with the transitions still remains.

2.6. Key issue 6: Change in transition probabilities at Week 52

The EAG scenario assumed that post-assessment transition probabilities to be the same as pre-assessment transition probabilities given there is high uncertainty associated with treatment response; this uncertainty impacts the patient numbers and hence the post-response transition probabilities. The EAG acknowledges that this assumption is not perfect or necessarily reflective of a realistic scenario but could be seen as a conservative step towards providing plausible bounds around the uncertainty associated with the treatment response definition and, in turn, with the post-response transition probabilities after 52 weeks.

2.7. Key issue 7: Hospitalisation rate for biologics other than tezepelumab may be overestimated

The EAG noted that the revised company base case implemented the EAG's suggestion that the hospitalisation rate for other biologics to be assumed same as tezepelumab thereby preventing simultaneous application of multiple treatment effects. Though this assumption is conservative and avoids counting the treatment effect more than once, the EAG acknowledges that in real clinical practice the actual hospitalisation rates might vary among the biologics.

2.8. Key issue 8: Asthma mortality may have been overestimated

The company's TE response indicated that the population considered in the ONS 2020 asthma mortality data and the Health Survey for England 2018 asthma report is less severe than the population of interest for tezepelumab, thereby underestimating the number of deaths occurred. However, the EAG is of the opinion that if the deaths would be higher in a severe asthma population, so would be the hospital admissions following exacerbations. Therefore, the resultant proportions are likely to be similar. Further, the asthma mortality in this model is already linked to exacerbations. In other words, for a more severe asthma population there would be more exacerbations which would in turn lead to an increase in the asthma mortality rate (i.e., an increase which is already accounted for in the model).

In addition, the EAG notes that the company has cited the percentage of deaths in patients aged <70 from a French study[4], which might not be generalisable to the UK population. In contrast, the data sources that EAG has considered, though not perfect, were all representative of the UK asthma population.

Moreover, the EAG's approach for deriving the probabilities is consistent with the approach in previous appraisals (particularly TA 565[3]) with the only difference being the use of latest data. This approach is also similar to studies like Watson et al.[5] where the the data were extracted for ICD codes J45 and J46 as well. The EAG further notes that patients enter the exacerbation state in every cycle in the model; and, because the asthma mortality is linked to exacerbations, it also applies to every cycle despite being modelled discretely.

Nevertheless, the EAG acknowledges the uncertainty associated with asthma mortality data across different sources and the heterogeneity among those studies. Therefore, the EAG has considered an additional scenario where the approach taken by EAG in TA 565[3] using the data from British Thoracic Society (BTS) adult asthma audit report (2016)[6] has been replicated (despite being relatively older data as compared to the ONS 2020[7] asthma mortality data used in the EAG base case). The EAG is of the opinion that the more plausible asthma mortality estimates are likely to be between the EAG base case and this scenario. Please see Section 3.2 for results of this additional EAG scenario.

2.9. Key issue 9: Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events

The company has indicated that the evidence supporting utility gains related to biologic treatment comes from the trial EQ-5D-5L data-derived utility regression and serves to circumvent the limitation of modelling asthma control as a dichotomous outcome (either controlled or uncontrolled). However, the EAG is of the opinion that the effectiveness of treatments should be reflected via modelled health states and adding additional utility with borderline statistical significance over and above the asthma control and exacerbations is not a manifestly legitimate modelling strategy. Moreover, neither the company's original submission nor the TE response provided the data used to derive the utility regression. Without visibility to the underlying data, the EAG is unable to access the credibility of company's argument in this regard further.

Additionally, the company mentioned in their TE response that the previous NICE appraisals (TA 565[3] and TA 278[8]) have considered the biologic treatment effect on utility. However, EAG noted that in both instances the biologic treatment effect related utilities were attached to the health states considered in the model structure. This is not the case in the current submission.

3. UPDATES TO THE COST-EFFECTIVENESS RESULTS

3.1. Company's revised base case results following TE (excluding NICE provided cPAS and CMU prices)

Table 3 below illustrates the changes made by the company in their base case following technical engagement and its alignment with EAG preference/base case. The differences between the company's revised base case and the EAG preference have also been described briefly.

Table 3: List of changes to company's base case following TE

	Company's original base case	Company's revised base case	EAG's preference	Alignment with EAG's preference
Exclusion of reslizumab as a comparator	Reslizumab not included as a comparator	Reslizumab included as a comparator and mepolizumab and benralizumab are considered comparators in resli-eligible population	Reslizumab included as a comparator and mepolizumab and benralizumab are considered comparators in resli-eligible population	Yes
Definition of treatment response	Any reduction in exacerbations or mOCS dose from baseline	Same	≥20% to ≥50% reduction in exacerbations based on clinical opinion to EAG	No
Mismatched subgroups and their provenance in network meta-analyses	subgroup NMA to use for comparisons with dupilumab is the EOS <300 cells/µL subgroup NMA	Same	EAG's clinical advice remains that the NMA for subgroup of patients with EOS ≥150 cells/µL is most appropriate for use in the comparison with dupilumab	No
Use of Asthma Control Questionnaire (ACQ) cut-off score to define controlled asthma	ACQ cut off = 1.5	Same	ACQ cut off = 1	No
Differentiation between 'controlled exacerbation' and 'uncontrolled exacerbation'	Different utilities for 'controlled' and 'uncontrolled' exacerbations	Equal utilities for 'controlled' and 'uncontrolled' exacerbations	Based on clinical opinion to EAG, not to differentiate between 'controlled' and 'uncontrolled' exacerbations and assign equal utility for both	Yes, partially

Change in transition probabilities at Week 52	Post-response assessment transition probabilities change from Week 53 onwards	Same	Owing to high uncertainty associated with the company's response definition, conservatively assume that transition probabilities do not change following response	No
Hospitalisation rate for biologics other than tezepelumab may be overestimated	Higher risk of hospitalization for biologics other than tezepelumab	Hospitalization rate for other biologics assumed to be the same as tezepelumab	Hospitalisation rate for other biologics to be assumed same as tezepelumab thereby preventing simultaneous application of multiple treatment effects	Yes
Asthma mortality may have been overestimated	Probabilities drawn from various sources based on data from 1981 to 2014	Same	Probabilities calibrated to approximate ONS 2020 data and HSE 2018 asthma report	No
Utility gain associated with biologic therapy, over and above treatment effectiveness and/or adverse events	[redacted] increase in utility from being treated with a biologic.	Same	No increase in utility from treatment with a biologic.	No

The company's revised base case results are shown in Table 4 to Table 8. It should be noted that these results include only the PAS price of tezepelumab and do not include the relevant confidential pricing information provided by NICE for the comparators and use the company-provided prices for SoC medications; they therefore do not reflect accurate treatment costs. Please see the appendix to this document, which contains results incorporating those discounts.

In addition, please note that the company did not provide the probabilistic results for the revised base case except for the reslizumab eligible population.

Further, for the anti-IL5 eligible and reslizumab eligible populations EAG noted that the company's revised fully incremental results were not based on the next non-dominated treatment option which has been corrected here.

Table 4: Company's revised base case results (anti-IL-5 eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 5: Company's revised base case results (dupilumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Dupilumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 6: Company's revised base case results (omalizumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
Omalizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 7: Company's revised base case results (non-bio eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: Company's revised base case results (reslizumab eligible)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Deterministic results					
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
Probabilistic results					
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

3.2. Results for EAG preferred assumptions following company's TE response (excluding NICE provided cPAS and CMU prices)

Results for the EAG preferred assumptions remain the same as given in the original EAG report except for the below:

1. EAG base case and scenario for reslizumab eligible population (as it now includes mepolizumab and benralizumab as comparators)
2. EAG's scenario with ACQ cut-off of 1 corrected using NPV (see Section 2.4 for further details)
3. Additional scenario for asthma mortality estimates based on EAG preferred assumption in TA565 (see Section 2.8)

The results for these revised assumptions have been provided in Table 9 to Table 12.

Please note that the results for the EAG preferred assumptions including cPAS and CMU prices have been provided in the appendix to this document.

Table 9: EAG base case results (reslizumab eligible)

	Discounted costs	**Discounted QALYs**	**Incremental discounted costs**	**Incremental discounted QALYs**	**Cost per QALY gained**
EAG deterministic base case					
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
EAG probabilistic base case					
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

Table 10: EAG scenario results (reslizumab eligible)

Preferred assumption	**Section in EAG original report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
Reslizumab eligible (Comparators: Mepolizumab+SoC, Benralizumab+SoC, Reslizumab+SoC)					
Company's revised base case	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	-
Benralizumab + SoC		[redacted]	[redacted]	Dominated	-
Reslizumab + SoC		[redacted]	[redacted]	Dominated	-
Re-estimated asthma mortality for people <75 years	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*455%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*447%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*457%*

Preferred assumption	**Section in EAG original report**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
No additional utility gain for being on biological treatment	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*3%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*3%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*3%*
No asthma mortality	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*>1000%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*>1000%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*>1000%*
Alternative transition probabilities					
a. Post-response assessment TP = Pre-response assessment TP	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-49%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-51%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*-48%*
b. Con Ex TP = Uncon Ex TP	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-11%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-11%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*-10%*
c. Asthma control state TP based on ACQ cut off =1 (company base case * 0.72)	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-2%*

Preferred assumption	Section in EAG original report	Incremental costs	Incremental QALYs	ICER £/QALY (tezepelumab+ SoC vs. comparator)	+/- company base case*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*-2%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*-2%*
Time horizon = 20 years	***Error! Reference source not found.***				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*31%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*31%*
Reslizumab + SoC		[redacted]	[redacted]	Dominated	*31%*

Table 11: Additional EAG scenario: Asthma mortality based on EAG preferred assumption in TA565

Preferred assumption	Section in EAG TE 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	*3.1*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	-
Benralizumab + SoC		[redacted]	[redacted]	Dominated	-
Asthma mortality per EAG preference in TA565	*2.8*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*6%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*3%*
Reslizumab eligible^ (Comparators: Mepolizumab+SoC, Benralizumab+SoC, Reslizumab+SoC)					
Company's revised base case	*3.1*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	-
Benralizumab + SoC		[redacted]	[redacted]	Dominated	
Reslizumab + SoC		[redacted]	[redacted]	Dominated	
Asthma mortality per EAG preference in TA565	*2.8*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*1%*

Preferred assumption	Section in EAG TE response	Incremental costs	Incremental QALYs	ICER £/QALY (tezepelumab+ SoC vs. comparator)	+/- company base case*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	
Reslizumab + SoC		[redacted]	[redacted]	Dominated	
Dupilumab eligible (Comparator: Dupilumab+SoC)					
Company's revised base case	*3.1*	[redacted]	[redacted]	Dominated	-
Asthma mortality per EAG preference in TA565	*2.8*	[redacted]	[redacted]	Dominated	*10%*
Omalizumab eligible (Comparator: Omalizumab+SoC)					
Company's revised base case	*3.1*	[redacted]	[redacted]	Dominated	-
Asthma mortality per EAG preference in TA565	*2.8*	[redacted]	[redacted]	Dominated	*13%*
Non-bio eligible, 3+ exacerbations or mOCS (Comparator: SoC)					
Company's revised base case	*3.1*	[redacted]	[redacted]	[redacted]	-
Asthma mortality per EAG preference in TA565	*2.8*	[redacted]	[redacted]	[redacted]	*8%*

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; Soc, Standard of Care

^Fully incremental analysis results are presented for Anti-IL5 and reslizumab eligible subgroups

Table 12: EAG scenario: ACQ cut off 1 (corrected results)

Preferred assumption	Section in EAG TE 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	*3.1*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	-
Benralizumab + SoC		[redacted]	[redacted]	Dominated	-
Asthma control state TP based on ACQ cut off =1 (company base case * 0.72)	*2.4*				
Mepolizumab + SoC		[redacted]	[redacted]	Dominated	*-3%*
Benralizumab + SoC		[redacted]	[redacted]	Dominated	*3%*

Preferred assumption	**Section in EAG TE response**	**Incremental costs**	**Incremental QALYs**	**ICER £/QALY (tezepelumab+ SoC vs. comparator)**	**+/- company base case***
Dupilumab eligible (Comparator: Dupilumab+SoC)					
Company’s revised base case	*3.1*	[redacted]	[redacted]	Dominated	-
Asthma control state TP based on ACQ cut off =1 (company base case * 0.72)	*2.4*	[redacted]	[redacted]	Dominated	*2%*
Omalizumab eligible (Comparator: Omalizumab+SoC)					
Company’s revised base case	*3.1*	[redacted]	[redacted]	Dominated	-
Asthma control state TP based on ACQ cut off =1 (company base case * 0.72)	*2.4*	[redacted]	[redacted]	Dominated	*1%*
Non-bio eligible, 3+ exacerbations or mOCS (Comparator: SoC)					
Company’s revised base case	*3.1*	[redacted]	[redacted]	[redacted]	-
Asthma control state TP based on ACQ cut off =1 (company base case * 0.72)	*2.4*	[redacted]	[redacted]	[redacted]	*1%*

4. EAG RESPONSE TO ADDITIONAL ISSUES/EVIDENCE

In response to technical engagement, the Company presented additional data from a longer-term, placebo-controlled, safety and efficacy study of tezepelumab for severe asthma (DESTINATION; NCT03706079). DESTINATION is an extension study to the NAVIGATOR and SOURCE trials, including 951 participants with severe asthma (827 from NAVIGATOR and 124 from SOURCE)[9]. Participants who were previously receiving tezepelumab 210 mg SC Q4W continued treatment, and those receiving placebo were randomised either to tezepelumab 210 mg SC Q4W or placebo. The primary outcomes in DESTINATION were adverse events over 104 weeks. The secondary outcome was AAER over 104 weeks.

The EAG note that data from DESTINATION were provided for information only and were not incorporated into analyses. Furthermore, no CSR or full text publication was provided, and as a result, the EAG was unable to crosscheck the data included in the Company's response. Additionally, no risk of bias assessment was provided by the Company for this new study, and the lack of available information precluded the EAG from conducting such an evaluation.

Briefly, the results reported by the Company are critiqued as follows:

- Commonly reported adverse events (AEs) with tezepelumab appeared to be similar in DESTINATION to NAVIGATOR and SOURCE: nasopharyngitis, upper respiratory tract infection, headache, asthma and bacterial bronchitis. The EAG highlight from the information provided by the Company that there was a [redacted] Due to a lack of published trial outputs, or a CSR. the EAG has been unable to confirm this. However, the EAG do agree with the Company that [redacted]

- In the earlier studies tezepelumab trials reported in the original Company submission, only one death occurred in a participant receiving tezepelumab (in SOURCE) but this was not considered to be due to study treatment. Over 104 weeks, the data provided for DESTINATION showed [redacted] Consistent with the earlier death in SOURCE, the Company state in their technical engagement response that none of the deaths in DESTINATION were considered to be causally related to tezepelumab. Again, there was no CSR provided to enable verification of these data.

- For AAER resulting in hospitalisations or emergency department visits, the Company state that [redacted] Again, these data could not be verified and it should also be considered that there has been no risk of bias assessment conducted for this study.
- The Company also stated in their technical engagement response that, in DESTINATION, tezepelumab "resulted in sustained improvements in reductions in exacerbations, improved lung function, symptom control and HRQoL." However, apart from the AAER data mentioned above, no data were provided to support this statement.

5. EAG RESPONSE TO ISSUES RAISED BY STAKEHOLDERS

Responses to technical engagement were received by the following stakeholders:

- British Thoracic Society (BTS)
- NHS England Specialised Commissioning
- British Society for Allergy & Clinical Immunology (BSACI)
- Asthma + Lung UK

EAG Response:

EAG thanks the stakeholders for their comments and highlighting the error in EAG report. The EAG agrees with the correction suggested by BTS and NHS England Specialised Commissioning i.e., other biologics are administered subcutaneously (Section 4.2.4, EAG report).

BSACI provided a range of comments on the likely impact of tezepelumab on the treatment pathway, and a consideration of likely effectiveness patterns. No specific implications for the EAG's modelling were identified.

Finally, Asthma + Lung UK provided a range of reflections on the impact of biologic treatments for patients' quality of life. No specific implications for the EAG's modelling were identified.

6. REFERENCES

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