NICE National Institute for Health and Care Excellence

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** from Astrazeneca
   - **a.** Company evidence submission summary for committee
   - **b.** Company evidence submission
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).

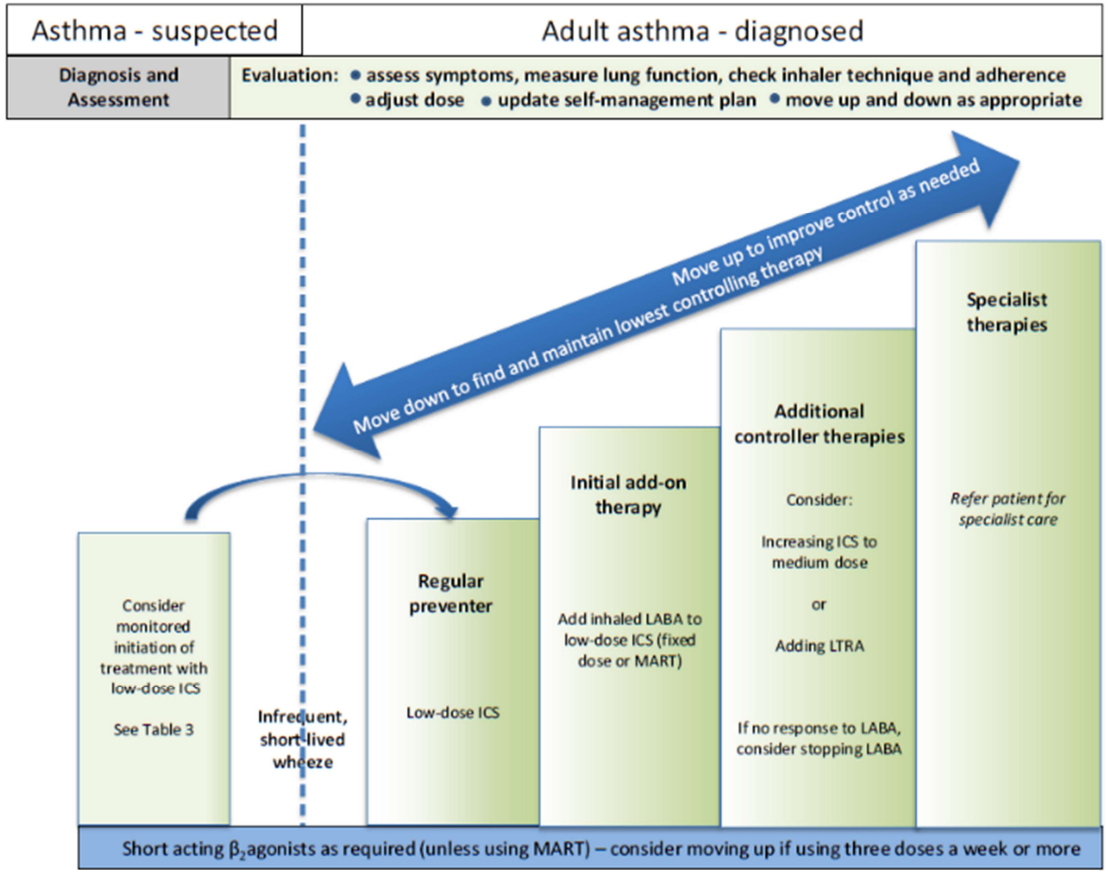
The burden of severe, uncontrolled asthma is high due to associated exacerbations and hospitalisations (5). The unpredictability and distress associated with severe, uncontrolled asthma symptoms has a substantial negative impact on the lives of patients, including a detriment in the ability to perform 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).

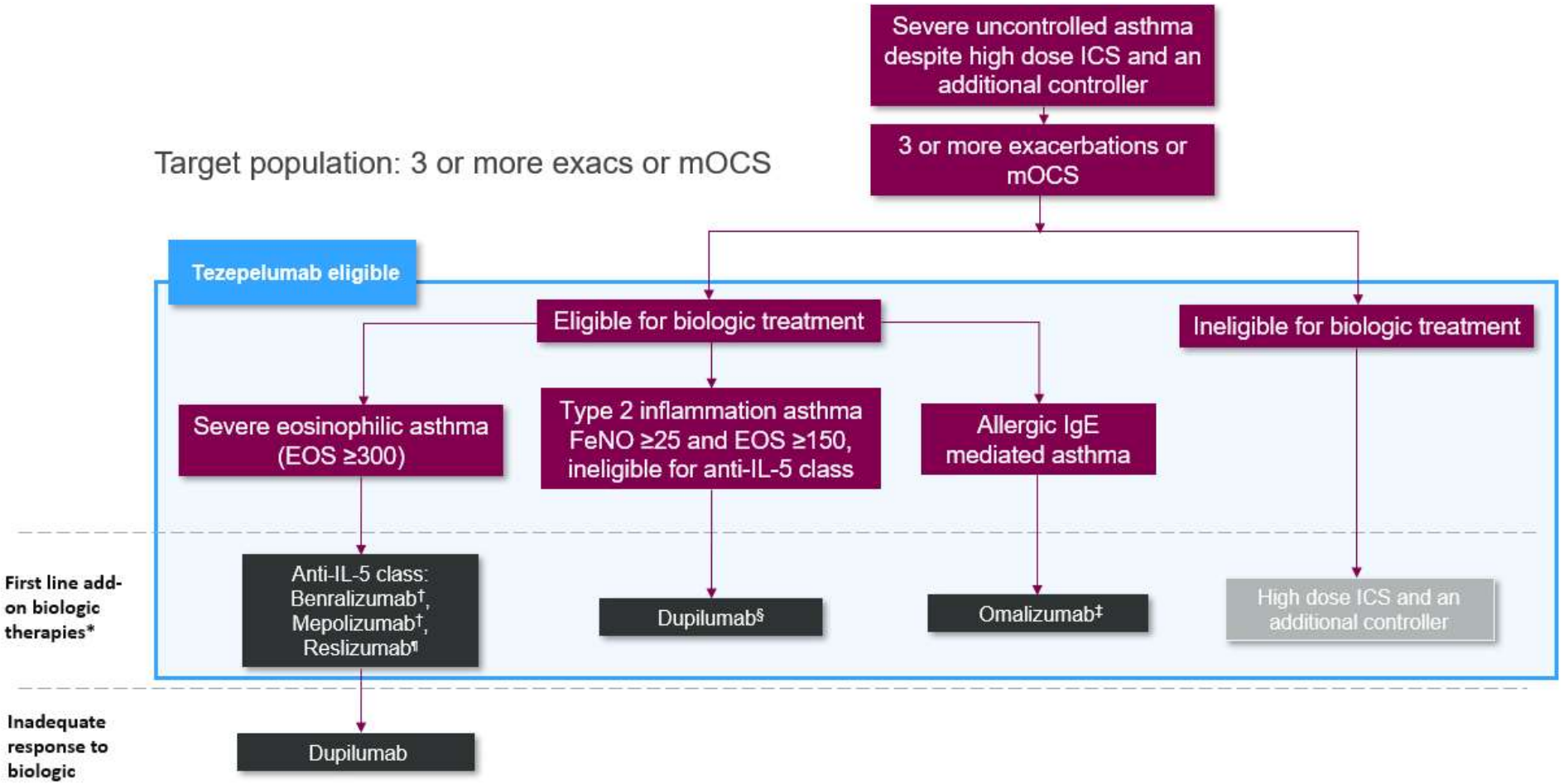
Figure 2 outlines the proposed positioning of tezepelumab within the biologic therapy pathway of care for severe asthma patients. The company submission positions tezepelumab as a treatment for adults and adolescents 12 years and older with severe uncontrolled asthma patients despite high dose ICS and 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)

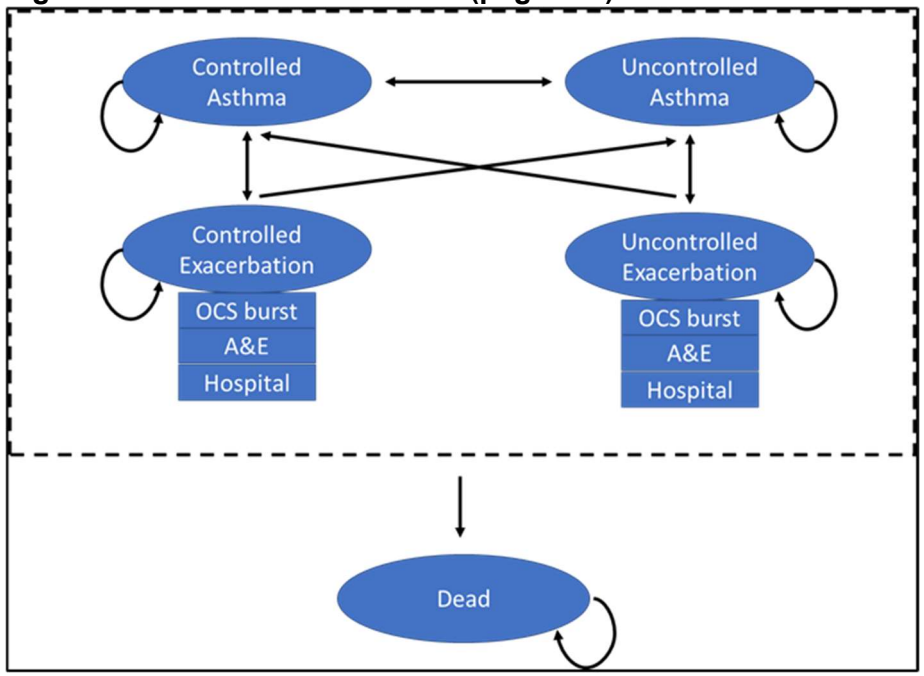
The economic evaluation assessed the cost-effectiveness of tezepelumab as an add-on to SoC and (in totality) considered patients with severe uncontrolled asthma despite high dose ICS and an additional controller, who experienced 3 or more exacerbations in the prior year, or who are on mOCS. The modelled 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

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)

Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID3910_Tezepelumab_Document B_[ACIC Fully Redacted]	**V1.0**	**Yes**	**20th May, 2022**

Contents

Tables and figures

Abbreviations

A&E	Accident and Emergency
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire 6-item
AE	Adverse event
AER	Asthma exacerbation rate
AERR	Asthma exacerbation rate reduction
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
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CFB	Change from baseline
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CrI	Credible interval
DIC	Deviance Information Criteria
ECG	Electrocardiogram
EOS	Eosinophil
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L/5L	European Quality of Life-5 Dimensions-3 Levels/5 Levels
ER	Emergency room
Exacs	Exacerbations
FAS	Full analysis set
FDA	US Food and Drug Administration
FEIA	Fluorescent enzyme immunoassay
FeNO	Fractional exhaled nitric oxide
$FEF_{25–75\%}$	Forced expiratory flow over 25–75% of the vital capacity
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E

IL	Interleukin
ITT	Intent-to-treat
IU	International Unit
IWRS	Interactive Web Response System
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LS	Least squares
LTRA	Leukotriene receptor antagonist
LY	Life years
LYG	Life years gained
mOCS	Maintenance oral corticosteroid treatment
MMRM	Mixed-effects model for repeated measures
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
OCS	Oral corticosteroid
OR	Odds ratio
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
PN	Predicted normal
ppb	Parts per billion
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
RCT	Randomised controlled trial
SABA	Short-acting beta agonist
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
SUCRA	Surface under the cumulative ranking
teze	Tezepelumab
TSLP	Thymic stromal lymphopoietin
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire
WTP	Willingness to pay

Glossary

Table 1: Glossary endpoints assessed in the NAVIGATOR, PATHWAY, and SOURCE trials and terms used in dossier

Endpoint	Explanation
AAER	The AAER is a measure of the number of asthma exacerbations per patient-year. Asthma exacerbations are episodic flare-ups of asthma, characterised by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness, and progressive decrease in lung function. Exacerbations carry a significant morbidity burden for patients and may be life-threatening (1). In the PATHWAY and NAVIGATOR trials, an asthma exacerbation was defined as a worsening of asthma that led to any of the following: • 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 • An ER 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
ACQ-6	The ACQ-6 is a validated instrument that measures asthma control. It features six questions on asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and beta-agonist use. Each question is scored from 0–6 with the total score being the average of the questions. The ACQ score ranges between 0 (well controlled) and 6 (extremely poorly controlled) (2). Mean ACQ-6 scores of ≤0.75 indicate well-controlled asthma, scores >0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates uncontrolled asthma (3). Individual changes of at least 0.5 are considered clinically meaningful (4).
AQLQ(S)+12	The AQLQ(S)+12 is an asthma-specific measure of HRQoL valid for use in patients aged 12–70 years. The questionnaire comprises four separate domains: symptoms (11 items), activity limitations (12 items), emotional function (5 items), and environmental stimuli (4 items). Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (not impaired at all) to 1 (severely impaired). The overall score is calculated as the mean response to all questions. The minimally important difference for the AQLQ(s)+12 is a change in score of 0.5 for overall quality of life and for each of the domains (5).
ASD	The ASD was used in the NAVIGATOR and SOURCE trials, and was completed by subjects twice daily. The ASD consists of 10 items. Five morning items assess night-time symptom severity in relation to: wheezing, shortness of breath, cough, chest tightness, and the frequency of night-time awakening. Five evening items assess daytime symptom severity in relation to: wheezing, shortness of breath, cough, chest tightness, and activity limitation since waking. Items are scored from 0 (no symptoms, no night-time awakening, or no activity limitation) to 4 (very severe symptoms, unable to sleep, or extreme activity limitation). Scores for wheezing, shortness of breath, cough, and chest tightness range from 'none' to 'very severe'. Responses for all 10 items are required to calculate the daily ASD score. A 7-day average asthma symptom score can be calculated based on the mean of at least four of the seven daily ASD scores. The 7-day average ASD score ranges from 0–4. Individual changes of at least 0.5 are considered clinically meaningful, and subjects experiencing a change of at least 0.5 are considered responders (6).
CGI-C/PGI-C	CGI-C and PGI-C (also known as CGI-I and PGI-I) evaluate change from the initiation of treatment from the clinician and patient perspective, respectively, on a 7-point categorical response scale ranging from 1 (very much improved) to 7 (very much worse) (7, 8).
EQ-5D-5L	The EQ-5D-5L is a standardised instrument used as a measure of health outcome, primarily designed for self-completion by respondents. The EQ-5D-5L questionnaire assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect

Endpoint	Explanation
	increasing levels of difficulty. The questionnaire also includes a VAS, where the subject is asked to rate current health status on a scale of 0–100, with 0 being the worst imaginable health state (9).
$FEF_{25–75\%}$	The $FEF_{25–75\%}$ is the mean forced expiratory flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled. $FEF_{25–75\%}$ is a measure of pulmonary function, and impairment of $FEF_{25–75\%}$ is considered to be an early marker of airway obstruction (10).
PEF	The PEF (also known as peak flow or peak flow rate) is the maximal rate at which a patient can exhale following maximal inhalation and is a measure of pulmonary function that correlates with FEV_1. Short-term PEF monitoring may be used to assess response to treatment, evaluate triggers for worsening symptoms, or to establish a baseline. Excessive variation in PEF suggests suboptimal asthma control and increases the risk of exacerbations (1).
Pre-BD FEV_1	Pre-BD FEV_1 is the volume of air a patient can exhale in 1 second following maximal inhalation, prior to the administration of a bronchodilator. Pre-BD FEV_1 can be used to assess the severity of obstructive lung diseases, such as asthma, by comparing with predicted FEV_1 value. Pre-BD FEV_1 can also be used to assess the patient's response to bronchodilators by comparing with post-BD FEV_1, known as the reversibility test or bronchodilator test (11).
Severe asthma	Severe asthma is defined as asthma that requires high dose ICS in combination with a long acting beta-agonist (ICS-LABA) to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimised treatment with high dose ICS-LABA (1).
SGRQ	The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in patients with diseases of airways obstruction (12). Scores are calculated for three domains: symptoms (frequency and severity), activities (that cause or are limited by breathlessness), impacts (social functioning and psychological disturbances resulting from airways disease). A total score is calculated from the three domain scores. Scores range from 0–100, with higher scores indicating more limitations. A minimum change in score of 4 units is considered clinically relevant (13).
Uncontrolled asthma	Uncontrolled asthma is defined as one or both of the following (1): • Poor symptom control (frequent symptoms or reliver use, activity limited by asthma, might waking due to asthma) • Frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalisation

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; CGI-C, Clinician Global Impression of Change; CGI-I, Clinician Global Impression of Improvement; ER, emergency room; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; $FEF_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HRQoL, health-related quality of life; OCS, oral corticosteroid; PEF, peak expiratory flow; PGI-C, Patient Global Impression of Change; PGI-I, Patient Global Impression of Improvement; SCS, systemic corticosteroid; SGRQ, St George's Respiratory Questionnaire; VAS, Visual Analogue Scale.

Executive summary

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation, with a subset of patients suffering from severe asthma which remains uncontrolled despite high dose inhaler therapies

Asthma is 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).

Inhaled corticosteroids (ICS) are first-line therapy for all patients with persistent asthma, controlling asthma symptoms and preventing exacerbations (14). The majority of patients can achieve the goal of well-controlled asthma with ICS treatments. Severe asthma is defined as asthma that requires high dose ICS in combination with a long acting beta-agonist (ICS-LABA) to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimised treatment with high dose ICS-LABA (1). Of the 5.4 million patients receiving treatment for asthma in the UK (15), it is estimated that around 4% have severe asthma (16), of which 65.5% (or 141,000 people) have severe, uncontrolled asthma (17).

The burden of severe uncontrolled asthma remains high due to associated exacerbations, hospitalisations and excess mortality (18)(24)

Severe uncontrolled asthma places substantial burden on patients and healthcare systems. 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, 19, 20) and negatively impacts their mental health (21).

In a 2015 UK study using asthma registry data from 2012, the healthcare costs per patient with severe asthma were higher than that for type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD) (1, 22). The cost burden is mainly driven by the number of exacerbations and hospitalisations, which is three-fold higher in severe uncontrolled asthma compared with non-severe, uncontrolled asthma (18). In a 2017 UK study using data from a nationally representative primary care database (OPRCD), the average healthcare costs per person per year with severe asthma ranged from £2,603 to £4,533 (23).

Patients with severe asthma have a higher mortality rate compared with patients with asthma (24). A 2019 analysis of 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 (25).

Despite the availability of biologics for severe asthma, a significant unmet need exists for a first-line biologic treatment with efficacy across phenotypes and biomarker profiles, to enable more patients with severe, uncontrolled asthma to achieve disease control and reduce the frequency of exacerbations, hospitalisations, and oral corticosteroid (OCS) use

The inflammatory cascade of severe uncontrolled asthma is complex and heterogeneous. Current biologic agents mostly act on a single specific downstream inflammatory target like eosinophils (EOS), immunoglobulin E (IgE), or cytokines (IL-4, -5 or -13) (37, 38) and have demonstrated effectiveness in specific phenotypes of severe asthma defined by biomarker criteria (EOS ≥300: benralizumab, mepolizumab and reslizumab; IgE: omalizumab; fractional exhaled nitric oxide (FeNO) ≥25 and EOS

≥150: dupilumab). Therefore the full set of biological mechanisms driving a patient's asthma are unlikely to be addressed by currently recommended biologics (39) and patients who regularly exacerbate but do not exhibit the above biomarker criteria, do not have access to biologic therapy.

The full set of biological mechanisms driving a patient's asthma are unlikely to be addressed by currently recommended biologics (39). Furthermore, patients who regularly exacerbate but do not exhibit the above biomarker criteria, do not have access to biologic therapy.

Treatment with biologic therapies is currently recommended in England and Wales to reduce exacerbations, dependency on OCS, and improve asthma control. NICE's recommendations relate to subsets of the patient population with 3 or more exacerbations in the prior year OR who are on mOCS, and reflect the fact that existing biologics are only effective in subpopulations defined by biomarkers as indicated above.

Whilst existing biologic agents can be life-changing for some patients, others continue to experience uncontrolled disease, resulting in a high exacerbation frequency, limitations on daily life, and poor health-related quality of life (HRQoL), as well as substantial healthcare costs for healthcare systems (40, 41).

OCS, either as short courses or as maintenance treatment (mOCS), are widely used in patients who are ineligible for biologic treatment or in whom biologic therapy provides inadequate disease control (1, 26-28) however they are associated with short and long term adverse events leading to increased mortality (29, 30).

Short courses of OCS used for treatment of exacerbations are associated with adverse effects, including sleep disturbance, increased infection risk, and thromboembolism (1, 31). Cumulative overexposure to OCS can result in serious systemic adverse effects in both the short- and long-term, including osteoporosis, adrenal suppression, cardiovascular events, and diabetes (26, 28, 32-34), which increases the burden of uncontrolled asthma for patients and healthcare systems (1, 35, 36).

Therefore, there is a need for a biologic treatment option for those who are currently ineligible for existing biologics and an additional first line treatment option for those who are currently eligible for existing biologic therapies.

Tezepelumab is a first-in-class biologic which acts at the top of the asthma inflammatory cascade, blocking the activity of multiple downstream pathways therefore demonstrating efficacy in severe asthma patients across multiple phenotypes and irrespective of baseline levels of currently established biomarkers, EOS, FeNO, or specific IgE (42, 43). Furthermore, tezepelumab has also been shown to reduce the levels of FeNO, IL-4, IL-5, IL-13 and IgE

Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin (TSLP) which sits at the top of the asthma inflammatory cascade (39). Tezepelumab significantly reduces the rate of asthma exacerbations by up to 71% across all severe, uncontrolled asthma patients regardless of phenotype and irrespective of biomarker levels (42, 43). In addition, tezepelumab is currently the only biologic to demonstrate a reduction in airway hyperresponsiveness which is a clinically important and relevant outcome (44).

The pivotal evidence for tezepelumab for the treatment of severe asthma comes from two Phase 3 randomised controlled trials (RCTs), NAVIGATOR and SOURCE, and one Phase 2 RCT, PATHWAY. The NAVIGATOR trial showed that at Week 52, tezepelumab reduced annualised asthma exacerbation rate (AAER) by 56% (rate ratio [RR]: 0.44; 95% confidence interval [CI]: 0.37, 0.53; p<0.001). The

PATHWAY trial showed that, at Week 52, tezepelumab reduced AAER by 71% (RR: 0.29; 95% CI: 0.16,0.51; p<0.001). The SOURCE trial demonstrated that the cumulative odds of achieving a category of greater percentage reduction in OCS dose for daily maintenance at Week 48 with tezepelumab versus placebo were odds ratio (OR) of 1.28 (95% CI: 0.69, 2.35; p=0.43) (Results are contextualised in Section B.2.13.2.1).

This appraisal positions tezepelumab as a clinical and cost-effective treatment for adults and adolescents 12 years and older with severe uncontrolled asthma 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 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.

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.

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This 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 company submission.

Table 2: The decision problem

	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 • 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. See Section B.3.2.3.2 for further details.
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	As per scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Patient and clinician evaluation of response • Lung function • Mortality • Time to discontinuation • Adverse effects of treatment • Health-related quality of life		
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) • 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	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
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 B.1.4

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.

B.1.2 Description of the technology being appraised

Table 3: 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 marketing authorisation 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] 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; PAS, Patient Access Scheme; PASLU, Patient Access Scheme Liaison Unit; TSLP, thymic stromal lymphopoietin.
† Subject to approval.

B.1.3 Health condition and position of the technology in the treatment pathway

SUMMARY

- Asthma is a heterogenous disease, usually characterised by chronic airway inflammation. It is 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)
- Whereas most asthma patients achieve disease control with standard of care, a small subset of patients have severe asthma defined as asthma that requires high dose ICS-LABA to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimised treatment with high dose ICS-LABA (1)
- Patients with severe, uncontrolled asthma have a high risk of exacerbations, defined as a progressive worsening of asthma symptoms and lung function impairment (1). Asthma exacerbations can be life-threatening and may require emergency care and hospitalisation (45, 46)
- Treatment with biologics, including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab, is recommended in patients with severe, uncontrolled asthma despite optimised care, with the choice of biologic prescribed depending on asthma phenotype and biomarker profile (1, 47)
- Current biologic therapies for severe, uncontrolled asthma are targeted to single or downstream eosinophilic and allergic inflammatory pathways (see Figure 1); however:
  - A high number of patients are ineligible for biologic therapy as they do not meet biomarker eligibility criteria
  - Over half of patients with severe asthma have uncontrolled or sub-optimally controlled asthma with their current biologic (40, 41)
  - If biologic therapy is not appropriate or ineffective, the main treatment option is OCS, either as short courses or as mOCS, which adds to the clinical burden due to the association of mOCS with adverse events (1, 26, 35, 36)
- Despite the availability of biologics for severe asthma, a significant unmet need exists for a first-line biologic treatment with efficacy across phenotypes and biomarker profiles, to enable more patients with severe, uncontrolled asthma to achieve disease control and reduce the frequency of exacerbations, hospitalisations, and OCS use
- Tezepelumab is a first-in-class anti-TSLP monoclonal antibody (48)

- TSLP is an upstream epithelial-derived cytokine that is released at the top of the inflammatory cascade in response to insults. TSLP activates multiple downstream pathways that are involved in airway inflammation and bronchial hyperresponsiveness in asthma (39, 48, 49)
- By blocking TSLP, tezepelumab thus exerts its therapeutic effect at the top of the inflammatory cascade delivering efficacy across asthma phenotypes and irrespective of biomarkers, including allergic, non-allergic, EOS-high, and EOS-low populations (42) as per the anticipated licensed indication
- This appraisal positions tezepelumab as a treatment for 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 who are on mOCS, irrespective of biomarker values

B.1.3.1 Asthma overview

Asthma is a heterogenous disease, usually characterised by chronic airway inflammation. It is 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). Progressive pathologic airway remodelling may occur, resulting in partially reversible or irreversible airway obstruction (50, 51).

B.1.3.2 Severe, uncontrolled asthma

Asthma presents in varying degrees of severity, ranging from mild, intermittent disease to severe asthma with debilitating, even life-threatening, symptoms (1). The majority of asthma patients are adequately controlled on standard of care but a subset continue to have uncontrolled asthma (1). According to the Global Initiative for Asthma (GINA) 2022 guidelines (1) and the ERS/ATS 2014 guidelines (52), severe asthma is defined as asthma that requires high dose ICS in combination with a long acting beta-agonist (ICS-LABA) to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimised treatment with high dose ICS-LABA.

Asthma control is assessed on the basis of symptom control and future risk of adverse outcomes (1, 52). 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 GINA guidelines) thus defines a patient with severe, uncontrolled asthma:

- Poor symptom control:
  - ACQ consistently ≥1.5 or Asthma Control Test (ACT) <20

  - Frequent symptoms, activity limited by asthma, night waking
  - Frequent rescue reliever use
- Frequent severe exacerbations (≥2/year) requiring a short course (≥3 days each) of mOCS
- Serious exacerbations requiring hospitalisation (≥1/year; see also Section B.1.3.4.1).

B.1.3.3 Epidemiology of severe, uncontrolled asthma

Asthma affects children and adults of all ages and is one of the most common chronic diseases with an estimated 262–339 million people affected worldwide (1, 53, 54). Estimates of the proportion of people with asthma who have severe, uncontrolled asthma vary considerably, ranging from 1.8 to 49.2% according to a 2018 systematic literature review, depending on geographic location and diagnostic criteria used (55).

In the UK, there are an estimated 5.4 million people receiving treatment for asthma (15). Of these, it is estimated that around 4% have severe asthma (16), of which 65.5% (or 141,000 people) have severe, uncontrolled asthma (17).

B.1.3.4 The burden of severe, uncontrolled asthma

Severe, uncontrolled asthma is associated with greater clinical, humanistic, and economic burden than non-severe asthma, or asthma that responds to treatment (1, 18, 19, 21, 23, 25, 40, 41, 45, 46, 55-71).

B.1.3.4.1 Clinical burden

Patients with severe, uncontrolled asthma are at high risk of exacerbations, which are potentially life-threatening with a possible need for emergency care (45, 56). An asthma exacerbation is defined as progressive worsening of asthma symptoms, such as shortness of breath, wheezing, cough, and chest tightness. During an exacerbation, lung function is impaired, manifesting as reduced peak expiratory flow (PEF) rate and forced expiratory volume in the first second (FEV_1) (1). An exacerbation can be triggered by a wide range of risk factors, including respiratory viral infections, bacteria, environmental allergens (e.g. mould), and other factors such as tobacco smoke and exhaust fumes (57).

Severe, uncontrolled asthma is associated with a high frequency of exacerbations. CPRD data from the UK have shown that the exacerbation rate in severe, uncontrolled asthma is 11 times higher than that of patients without severe, uncontrolled asthma (mean annual exacerbation rate per patient year: 1.088 [95% CI: 1.002, 1.181] versus 0.098 [95% CI:

0.096, 0.100], respectively) (58). AstraZeneca is presently sponsoring the NOVELTY study, an observational study of patients with asthma that aims to describe patient characteristics, treatment patterns, and disease burden over time. In NOVELTY, over the 12-month baseline period, [redacted] of patients defined as having severe, controlled asthma had no exacerbations compared with [redacted] of patients with severe, uncontrolled asthma. Furthermore, [redacted] of patients with severe, uncontrolled asthma had ≥3 exacerbations (59).

Asthma exacerbations are associated with a high mortality rate therefore patients with asthma have a higher mortality rate compared with patients with asthma (24). A 2007 database study in the UK (N=250,043 asthma admissions) reported a mortality rate of 858 (95% CI: 750, 977) per 100,000 hospital admissions for acute severe asthma between 2000 and 2005 (not including emergency room [ER] visits); critical care unit admissions had a higher mortality rate of 3,591 per 100,000 (95% CI: 2,207, 5,491) (45). Similarly, a database study in Scotland collecting data on hospitalisations for asthma (N=116,457) between 1981 and 2009 reported that 0.9% (n=1,000) of hospitalisations resulted in death within 30 days of admission (46). It is well documented that patients who have severe asthma as result of frequent exacerbations have a higher mortality rate compared with patients with asthma (24, 45, 46). In England and Wales, deaths resulting from asthma are increasing. A 2019 analysis of ONS data by Asthma UK revealed that more than 1,400 adults and children died from asthma attacks in 2018, an 8% increase since 2017 (25). 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 (25).

In addition to the burden of exacerbations, a broad range of non-respiratory and respiratory comorbidities are commonly reported in the severe, uncontrolled asthma population; these include hypertension, allergy, type 2 diabetes, COPD, and chronic sinusitis (60-64).

The burden of OCS use in severe uncontrolled asthma

In patients for whom biologic therapy provides inadequate disease control, or in patients who are ineligible for biologic treatment, OCS, either as short courses or as mOCS, are the main treatment option (1, 26-28). Patients with severe, uncontrolled asthma and frequent exacerbations are more likely to require frequent mOCS compared with those with moderate disease (27). Short- or long-term mOCS use is associated with the risk of

becoming mOCS-dependent, i.e. unable to achieve asthma control without mOCS (72). According to a recent (2021) study of UK patients with severe asthma in the UK Severe Asthma Registry, 59.9% of patients on biologics were receiving mOCS (73).

Short courses of OCS used to treatment of acute exacerbations are also associated with adverse effects, including sleep disturbance, increased infection risk, and thromboembolism (1, 31). A study investigating adverse outcomes from OCS use in asthma over a 2-year follow up period found that only 2–4 short courses of OCS at standard doses for treating an asthma exacerbation over a patient's lifetime was associated with an increased risk of adverse events (such as heart failure, type 2 diabetes, cataract, osteoporosis, and depression/anxiety). The study found that the onset of some adverse outcomes was associated with cumulative exposure of 0.5 to < 1 g of systemic corticosteroids, equivalent to only 4 lifetime courses (31). The current (2022) GINA guidelines recommend a short course (approximately 5–7 days) of OCS only for patients with an acute asthma exacerbation and do not recommend OCS as a long-term treatment due to the risk of adverse events (1). Cumulative overexposure to OCS can result in serious systemic adverse effects in both the short- and long-term, including osteoporosis, adrenal suppression, cardiovascular events, and diabetes (26, 28, 32-34), which increases the burden of uncontrolled asthma for patients and healthcare systems (1, 35, 36). Furthermore, long-term OCS use increases mortality risk in asthma patients (29, 30).

It follows that a treatment that prevents asthma exacerbations in patients with severe, uncontrolled asthma will therefore prevent patients from requiring OCS treatment (either short bursts or chronic use), along with the risks of OCS-dependency and OCS-related AEs it entails.

B.1.3.4.2 Humanistic and quality of life burden

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, 19). Several studies have shown lower HRQoL scores among patients with severe, uncontrolled asthma versus those with better disease control (55, 61, 65, 66); for example, European Quality of Life-5 Dimensions (EQ-5D) values of 0.728 versus 0.937 have been reported for patients with severe uncontrolled versus controlled asthma, respectively (67). Patients with severe, uncontrolled asthma experience more symptoms, night awakenings, rescue medication use, and activity

impairment than those with non-severe or controlled asthma (65). Furthermore, the vast majority of patients with uncontrolled asthma experience symptoms that affect at least 1 day per week, which is not seen in patients with controlled asthma (68).

Patients also often experience a negative impact on their mental health, with one study finding that 65.3% of patients with moderate-to-severe, uncontrolled asthma had anxiety and/or depression, as determined by the hospital anxiety and depression scale (HADS) (21). The humanistic burden is compounded by suboptimal disease control that can occur with currently approved biologics (40, 41), meaning that patients continue to experience limitations on daily life and exacerbations that impair their HRQoL.

Symptomatic asthma impacts on workplace productivity. In a global online survey completed by 1,598 working adults with symptomatic asthma (of which 300 were in the UK), respondents indicated that, on average, 9.3% of their working week was missed due to asthma (3.5% among UK subjects), and work productivity loss due to asthma was 36% (21% among UK subjects) (20).

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 (74).

B.1.3.4.3 Economic burden

Management of severe, uncontrolled asthma places a substantial economic burden on healthcare systems. Despite affecting the minority of the total asthma population (≤5%), severe, uncontrolled asthma accounts for 40% of all direct costs in asthma (69). The cost burden is mainly driven by the number of exacerbations and hospitalisations, which is three-fold higher than in non-severe, uncontrolled asthma, as well as the number of unplanned ER visits, which is twice that of non-severe, uncontrolled asthma (18). In a 2017 UK study using data from the OPCRD (a nationally representative primary care database), the average annual healthcare costs per person with severe asthma ranged from £2,603 to £4,533 (23). Asthma medication was the major driver of costs, with mOCS use and hospital inpatient visits identified as important additional cost drivers (23). In a 2018 UK cohort study enrolling 363,558 patients with active asthma, total mean per-patient healthcare resource use and associated costs were four times greater in patients with severe uncontrolled eosinophilic asthma versus that for all patients in the cohort (resource use and cost ratio: 3.9; 95% CI: 3.7, 4.1) (70). In a 2020 analysis of the US CHRONICLE

study, among 1,856 patients with severe asthma, 19% of patients required an ER visit and 12% of patients were hospitalised at least once due to asthma (at any point from 12 months prior to enrolment to each patient's latest data collection) with a mean hospital stay of 5 days (71). ICU admission was required in 14% of asthma hospitalisations, with a mean ICU stay of 4 days.

B.1.3.5 Asthma phenotypes and the role of TSLP in the pathophysiology of asthma

Asthma is a heterogenous disease, and patients with similar clinical presentations are described as having the same 'phenotype'. Clinical phenotypes are typically based on asthma history and well-defined clinical characteristics, such as age of onset and allergic or non-allergic status (75, 76).

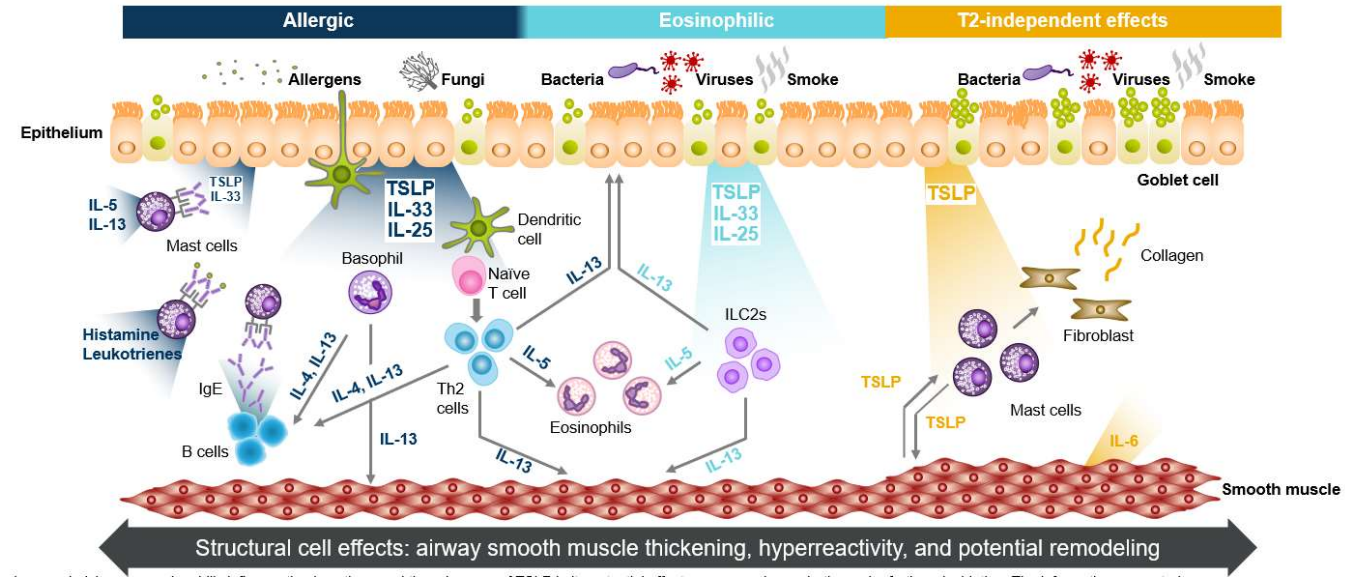
The variable clinical presentations observed in asthma are driven by different biological mechanisms, and with the advent of current biologic treatments, inflammatory phenotypes have more recently been used to describe asthma populations grouped together by either biomarker expression or perceived underlying inflammatory biology. Key biomarkers include serum specific IgE, blood (and sputum) EOS, and FeNO (1, 75, 77). Key inflammatory phenotypes include allergic (atopic), eosinophilic, and non-eosinophilic asthma (e.g. neutrophilic or paucigranulocytic asthma) (75). Allergic asthma is confirmed by positive allergy skin tests and/or increased levels of the biomarker serum specific IgE, whilst eosinophilic asthma is characterised by an increase in blood (and sputum) EOS (75).

The IgE, EOS, and FeNO biomarkers are currently used to define different subtypes of asthma, as they are indicative of distinct inflammatory pathways; these are central to the management of severe, uncontrolled asthma, as biologic treatments are prescribed on the basis of individual inflammatory pathways in current clinical practice (39, 48, 75). However, most severe, uncontrolled asthma patients are positive for one or two of these key biomarkers, but relatively few patients are either positive or negative for all three of these biomarkers (38, 78-80). This can indicate either the upregulation of multiple key inflammatory pathways or a lack of upregulation of these pathways. As a result, it is often unclear if a patient has an allergic phenotype, an eosinophilic phenotype, or neither phenotype (48).

Biomarkers (e.g. IgE, FeNO, sputum or blood eosinophils), when available, can help inform biologic selection but may not be specific enough to clearly identify an asthma phenotype and the biologic best suited to a patient (81). Therefore there is a need for a treatment option that works earlier on in the inflammatory cascade than existing biologics to provide optimal treatment regardless of inflammatory pathway.

TSLP is an upstream proinflammatory epithelial-derived cytokine that plays a central role in the initiation of airway inflammation in asthma, and initiates downstream inflammatory cascades in response to environmental insults as illustrated in Figure 1 (42, 48). The role of TSLP across phenotypes and biomarkers makes it an attractive therapeutic target for severe, uncontrolled asthma, since, by targeting TSLP, multiple downstream inflammatory pathways can be influenced (39, 77). Accordingly, the latest (2022) GINA guidelines were updated to include anti-TSLP as a new class of biologic therapy for severe asthma (1). TSLP as a therapeutic target in the treatment of severe, uncontrolled asthma is discussed further in Section B.1.3.9.1.

Figure 1: The role of TSLP in driving asthma inflammation



Abbreviations: IgE, immunoglobulin E; IL, interleukin; T2, Type 2; TSLP, thymic stromal lymphopoietin.
Source: Adapted from Gauvreau 2020 (48), Porsbjerg 2020 (82).

B.1.3.6 Treatment options for severe, uncontrolled asthma

Treatment with biologic therapies is currently recommended in England and Wales to reduce exacerbations, dependency on OCS and improve asthma control. NICE's recommendations relate to subsets of the patient population with 3 or more exacerbations in the prior year or who are on mOCS, and reflect the fact that existing biologics are only effective in subpopulations defined by biomarkers. In England and Wales, treatment for

severe, uncontrolled asthma generally follows the BTS/SIGN guidelines, which are summarised below alongside the relevant NICE technology appraisal guidance. GINA guidelines for difficult-to-treat and severe asthma are summarised in Section B.1.3.6.2.

B.1.3.6.1 UK guidelines

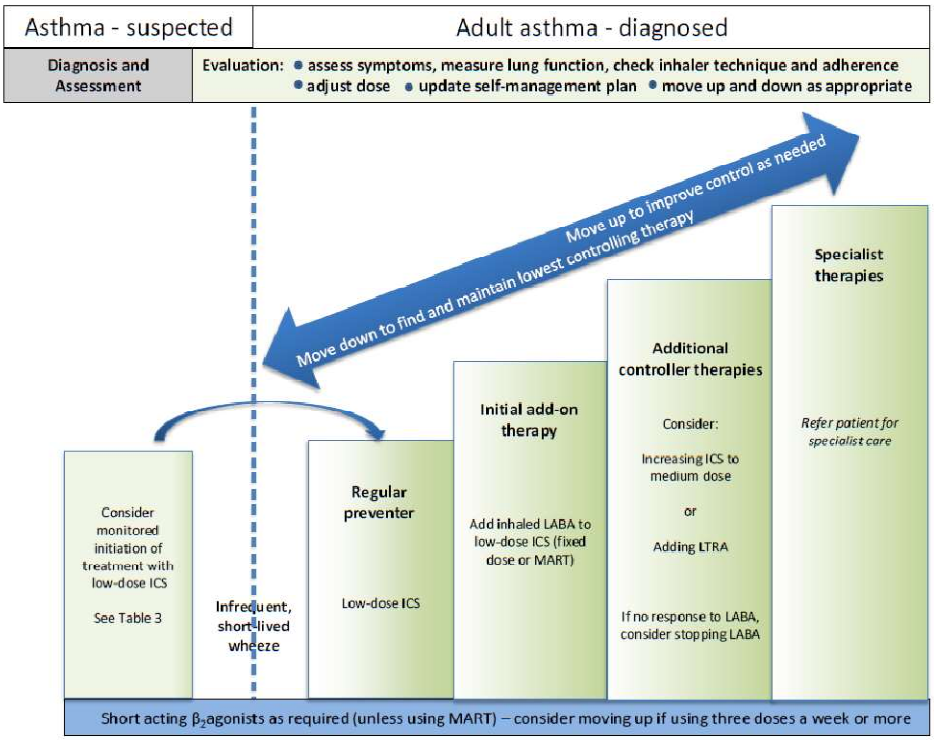
The aim of asthma treatment according to the BTS/SIGN guidelines (47) is to achieve disease control, with complete asthma control defined as:

- No daytime symptoms
- No night-time awakening due to asthma
- No need for rescue medication
- No asthma attacks
- No limitations on activity, including exercise
- Normal lung function (FEV_1 and/or PEF >80% predicted or best)
- Minimal side effects from medication

The guidelines define difficult asthma as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose inhaled corticosteroid (ICS) plus a long-acting beta agonist (LABA) or leukotriene receptor antagonist (LTRA); or medium-dose ICS plus a LABA or LTRA and an appropriate additional therapy (see below); or continuous or frequent use of oral steroids. It is recommended that patients with difficult asthma are systematically evaluated, including confirmation of an asthma diagnosis, identification of persisting symptoms, and assessment of therapy adherence.

Guidelines on the pharmacological management of asthma in adults and adolescents are summarised in Figure 2.

Figure 2: 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.

For adults and adolescents aged >12 years with an asthma diagnosis, short-acting bronchodilators (e.g. short-acting beta agonists [SABA], inhaled ipratropium bromide, and theophyllines) should be prescribed to relieve symptoms. ICSs are the first choice of preventer therapy, with the starting dose determined according to disease severity (usually a low dose for adults/adolescents). LTRAs, sodium cromoglicate, nedocromil sodium, and theophyllines may also be considered.

Add-on therapies may be required if asthma is not adequately controlled with low-dose ICS alone. Inhaled LABA is the first choice of add-on therapy in adults/adolescents. If there is an improvement when LABA is added but control remains suboptimal, the LABA can be continued and the dose of ICS increased to medium. If there is no improvement when a LABA is added, consideration should be given to stopping the LABA before increasing the dose of ICS. An alternative to increasing the ICS dose is adding a LTRA.

In adults with asthma that is not adequately controlled on the recommended initial or additional controller therapies (medium-dose ICS plus LABA or LTRA), specialist therapies should be considered:

- Increase ICS to high dose
- Add LTRA if not already tried, or
- Add tiotropium bromide, or
- Add a theophylline

For patients with a high mOCS burden, the following treatments may be considered:

- Omalizumab
- Mepolizumab, reslizumab, or benralizumab

Bronchial thermoplasty may be considered in cases of severe asthma that is poorly controlled despite optimal medical therapy.

For the management of acute asthma, the BTS/SIGN guidelines recommend using high-dose inhaled β2 agonists as first-line treatment in patients with acute asthma and intravenous β2 agonists if inhaled therapy cannot be used reliably. Steroids should also be administered in adequate doses to all patients with an acute asthma attack as early as possible.

Nebulised ipratropium bromide can be added to β2 agonist treatment for patients with acute severe or life-threatening asthma or those with a poor initial response to β2 agonist treatment. A single dose of intravenous magnesium sulphate should be considered for patients with acute severe asthma (PEF <50% best or predicted) who have not had a good initial response to inhaled bronchodilator therapy.

The NICE guidelines for the treatment of asthma (NG80) do not cover the management of severe asthma or acute asthma attacks (83), 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. This guidance is summarised in Table 4. NICE’s recommendations relate to subsets of the patient population with 3 or more exacerbations in the prior year OR who are on mOCS, and reflect the fact that existing biologics are only effective in subpopulations defined by biomarkers.

Note that NICE has also recently published a COVID-19 rapid guideline for severe asthma (NG166), which recommends that patients receiving biologic therapy should continue to do so, as these therapies do not suppress immunity (84).

Table 4: Summary of NICE technology appraisal guidance on biologics 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 (85)	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 (87)	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 (88)
Benralizumab Indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists (89)	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: • 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

Treatment and licensed indication (SmPC)	NICE recommendation
	• Blood EOS is ≥400 cells/µl with ≥3 exacerbations in the last 12 months needing SCS (that is, the person is eligible for reslizumab) (90)
Mepolizumab Indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (91)	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) (92)
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 (93)	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 (94)

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.

B.1.3.6.2 GINA 2022 guidelines

GINA recently (2022) updated its guidance for the management of difficult-to-treat and severe asthma (1). In patients with elevated Type 2 biomarkers despite high-dose ICS, non-biologics should be considered first given the high cost of biologic therapy. If available and affordable, use of an add-on Type 2-targeted biologic should be considered in "patients with exacerbations or poor symptom control despite taking at least high dose ICS-LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS". Recommended biologics include omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab.

Specific to tezepelumab, the GINA 2022 guidelines recommend tezepelumab treatment for severe asthma irrespective of biomarkers (1).

Response to biologic add-on therapy should be reviewed after the first 3–4 months and then every 3–6 months thereafter. In patients with a good response to Type 2-targeted biologic therapy, the guidelines recommend re-evaluating the need for asthma medication every 3–6 months. Consider first a gradual decrease or cessation of OCS due to their significant adverse effects, and then a reduction in ICS dose after 3–6 months; however, inhaled therapy should not be stopped completely.

B.1.3.7 Current treatment patterns in the UK

The UK Severe Asthma Registry (UKSAR) is the world's largest national severe asthma registry collecting standardised data on referrals to UK specialist services. A study of UKSAR data assessed biologic treatment patterns for 2,225 patients with severe asthma over the period November 2016 to February 2020 (73). 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. It should be noted 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.

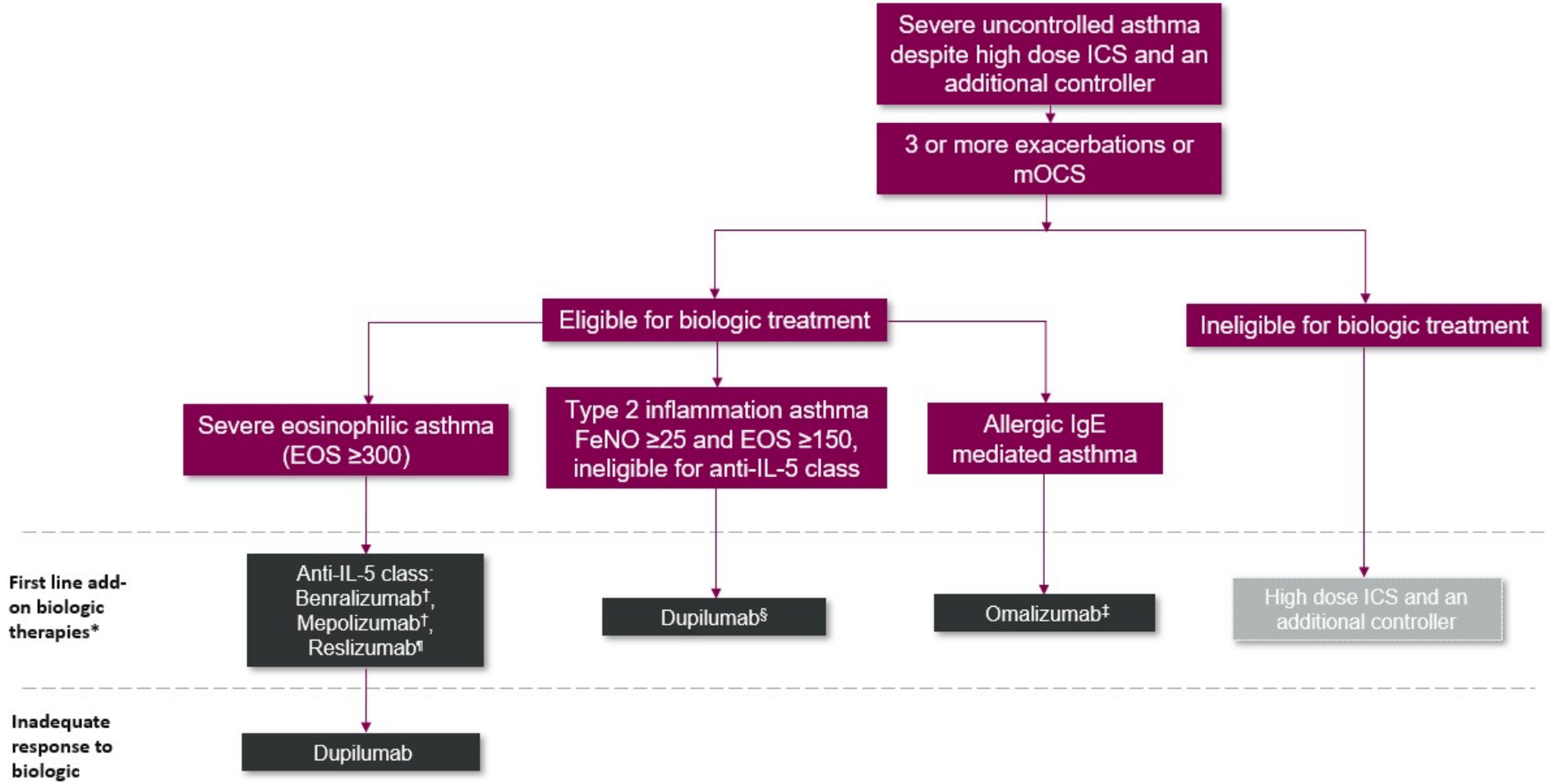
Table 5: Relative rates of prescribing of biologic therapies currently reimbursed in the UK for the treatment of severe asthma – Data from the UKSAR

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 (73).

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. An overview of available biologics and their respective eligible patient population (by biomarker profile) is presented in Figure 3. (See also Table 4, which summarises the licensed indications and NICE recommendation for each biologic).

Figure 3: Current treatment pathway for the target population



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.

B.1.3.8 Unmet needs in the treatment of severe asthma

Asthma is a heterogeneous disease driven by multiple inflammatory pathways, yet current biologic therapies for severe asthma are targeted to single pathways (37, 38). Therefore, the full set of biological mechanisms driving an individual patient's asthma are unlikely to be addressed by currently recommended biologics (39) leaving the following areas of unmet need:

- **There is a need for additional treatment options for those who are currently ineligible for existing biologic therapies:** A significant number of patients are ineligible for current biologic treatments, in part due to not having any clear driver of inflammation. As shown in Figure 3, patients without an allergic or eosinophilic asthma phenotype have no biologic therapy options, and thus a substantial proportion of patients with severe, uncontrolled asthma have a gap in their disease management options (39, 95). There remains a particular unmet need among the subgroup of severe, uncontrolled asthma patients with low eosinophils (<150 cells/μL) for whom there are no biologics available (96). AstraZeneca is currently conducting a real-world evidence study to demonstrate the burden of disease and unmet need in this patient subgroup compared with patients with high eosinophil counts/those who are eligible for biologic treatment. [redacted]. UK clinicians have also highlighted the need for effective treatment options specifically for patients who are on the cusp of the biologic eligibility criteria including those patients who fit the dupilumab biomarker eligibility criteria but are not on mOCS (96). There are more limited treatment options for adolescent patients compared with adult patients as benralizumab, mepolizumab and reslizumab are recommended only for adults. Having a treatment option that works well in the adolescent population will be valuable as currently only a small proportion are eligible for biologic therapy (96).
- **There is a need for additional first line treatment options for those who are currently eligible for existing biologic therapies:** An estimated 57% of patients with severe asthma who are treated with currently approved biologics remain sub-optimally controlled due to underlying inflammation that is left unaddressed by their current biologic treatment (40). These patients continue to experience uncontrolled disease, resulting in a high exacerbation frequency, limitations on daily life and poor HRQoL, as well as substantial healthcare costs for healthcare systems (40, 41). Due to persistent asthma symptoms and inability to taper or discontinue mOCS use, many

patients will be forced to switch biologic therapy; 34% of anti-IL-5 biologic-treated patients will switch to another biologic therapy (97). Clinicians highlighted that there are some patients, more so in adolescents, that have both allergic and eosinophilic asthma. More often than not they would be treated for the eosinophilic part of their asthma however these patients are often sub-optimally controlled as only part of the inflammatory pathway is being targeted. Therefore having a treatment that can target and treat both parts of the inflammatory cascade would be beneficial (96). Clinicians also mentioned that some patients on current biologic therapy develop antidrug antibodies and so there is a need for more treatment options (96).

For patients experiencing insufficient control of their exacerbations with existing biologics, or who are ineligible for existing biologics, their primary treatment option is OCS, either through frequent short courses or mOCS. Evidence suggests that mOCS overuse remains a frequent issue among the severe, uncontrolled asthma population (98, 99), leading to a further clinical burden to patients and increased healthcare use from the treatment of adverse effects such as osteoporosis, adrenal suppression, cardiovascular events, and diabetes (27, 32, 34-36). Asthma control is therefore very important to minimise risk of exacerbations and consequent requirement for either acute or chronic OCS use, which may progress to dependence with time. In line with this, the GINA 2022 guideline encourages careful day-to-day adjustment of controller therapy in order to reduce the risk of exacerbations requiring OCS (1).

A conclusion from the committee in the recent NICE TAG for dupilumab (TA751) states that “there is a need for new treatments with a different mode of action for people with severe asthma with Type 2 inflammation whose asthma does not respond with current standard care, and for people not eligible for current NICE recommended biologicals” (94). Expediting treatment initiation with a first-line biologic that is effective regardless of phenotype and irrespective of biomarkers would increase the number of patients eligible for a biologic therapy and remove the need to bridge the treatment gap with OCS use.

B.1.3.9 Tezepelumab in the clinical pathway of care

Tezepelumab is expected to meet unmet clinical needs in the treatment of severe asthma through its unique mechanism of action and efficacy across phenotypes, irrespective of biomarker levels (39, 42) as per the anticipated licensed indication. If recommended by NICE, tezepelumab will become the only biologic reimbursed in England and Wales that is

recommended for severe uncontrolled asthma patients with 3 or more exacerbations in the prior year or who require mOCS, irrespective of biomarkers or phenotypes.

B.1.3.9.1 Mechanism of action

Tezepelumab is a first-in-class anti-TSLP monoclonal antibody (48). The airway epithelium is the first point of contact for inhaled viruses, bacteria, allergens, smoke extract, and other environmental insults that can trigger asthma (42, 48, 100). TSLP is an upstream epithelial-derived cytokine that is released at the top of the inflammatory cascade in response to insults. TSLP activates multiple downstream pathways that are involved in airway inflammation and bronchi hyperresponsiveness in asthma (39, 48, 49).

Tezepelumab specifically binds to human TSLP with high affinity and prevents its interaction with the TSLP receptor complex on cells involved in the inflammatory response (39, 42, 48). This inhibits the inflammatory cascade and reduces initiation and persistence of downstream inflammatory responses (42, 48, 100). Tezepelumab inhibits the release of a broad range of cytokines (e.g., IL-5, IL-13) and biomarkers (e.g., EOS, IgE, and FeNO), showing that it inhibits multiple downstream inflammatory pathways via its blockage of TSLP. Tezepelumab's mode of action is a key differentiator from currently available biologic therapies for severe asthma which target single or downstream inflammatory pathways (39). Based on this, clinicians expect tezepelumab to have a similar degree of efficacy to current biologics but to be effective in a broader population as TLSP is at the top of the inflammatory cascade (96).

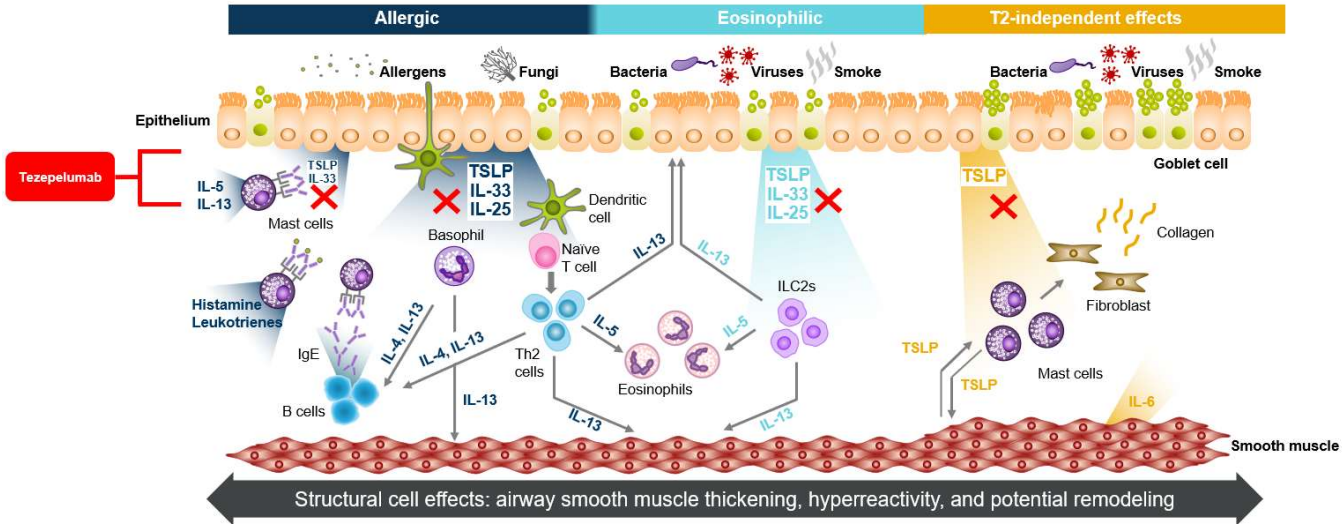
Clinicians also believe that by acting earlier on in the inflammatory cascade, it is likely that tezepelumab will enable dual treatment of those patients that have both allergic and eosinophilic asthma. Currently, these patients can only be treated with a biologic that only targets one component (normally eosinophilic part) and so sometimes are sub optimally controlled or have to switch treatment (96).

In addition, some clinicians acknowledge that as tezepelumab acts directly on the airway epithelia, they would expect its treatment failure rate to be lower than that of biologics as result of impact on airway hyperresponsiveness and other mechanistic effects of working higher in the inflammatory cascade. Current biologics either don't have data or have very poor data on airway hyperresponsiveness which is a very important endpoint in clinical practice, and a hallmark of asthma used to characterise disease diagnosis (96).

As a result of its novel mechanism of action, tezepelumab delivers efficacy across all severe, uncontrolled asthma patients regardless of their biomarker profile or phenotype (39, 42), addressing the needs of patients ineligible for existing biologic therapies and providing another treatment option for patients currently eligible for biologics.

The mechanism of action of tezepelumab is illustrated in Figure 4.

Figure 4: Tezepelumab mechanism of action



Abbreviations: IgE, immunoglobulin E; IL, interleukin; T2, Type 2; TSLP, thymic stromal lymphopoietin.
Source: Adapted from Gauvreau 2020 (48), Porsbjerg 2020 (82).

B.1.3.10 Tezepelumab positioning

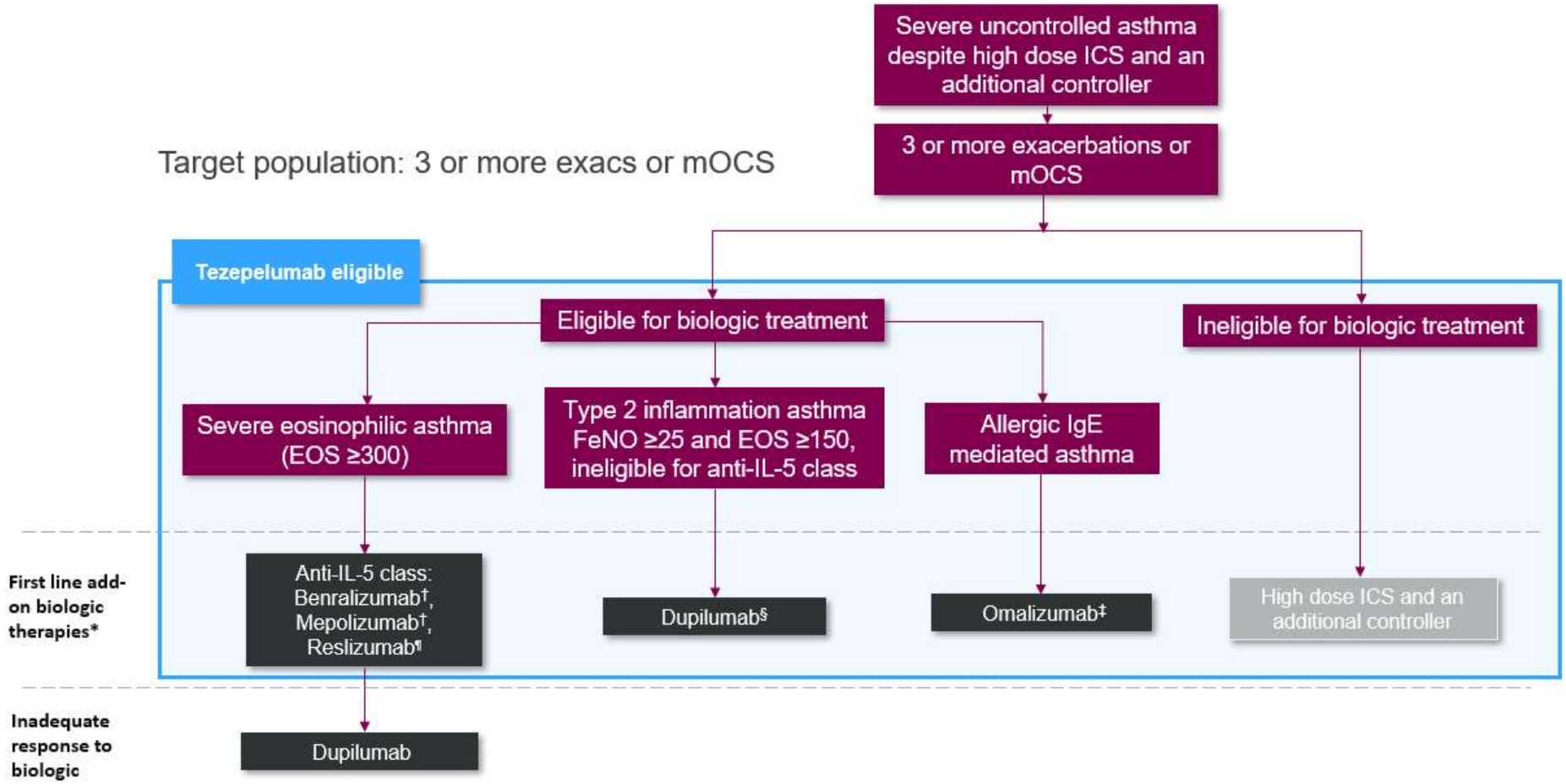
The inflammatory cascade of severe uncontrolled asthma is complex and heterogeneous. Current biologic agents mostly act on a single specific downstream inflammatory target like eosinophils (EOS), IgE, or cytokines (IL-4, -5 or -13) (37, 38) and have demonstrated effectiveness in specific phenotypes of severe asthma defined by biomarker criteria. Inflammation in severe asthma is complex, dynamic and heterogeneous. Patients with severe uncontrolled asthma often exhibit overlapping or changing phenotypes (37, 38, 101-104) and almost 15% of patients present with no defined inflammatory pathway (78). By exerting its effect at the top of the TSLP inflammatory cascade, tezepelumab delivers efficacy across asthma phenotypes and irrespective of biomarker levels as per the anticipated licensed indication (105). Providing access to tezepelumab in the 3 or more exacerbations or mOCS population will help simplify the treatment landscape and enable more patients to have access to biologic therapy. Insights leveraged from clinicians in the UK show that they unanimously agree in the value of having a biologic with a simpler and broader recommendation (96) (105). Introducing tezepelumab in this setting will provide

access to biologic therapy for some patients who are currently ineligible and will provide an alternative treatment option for patients who are currently eligible.

The pivotal evidence for tezepelumab for the treatment of severe asthma comes from two Phase 3 RCTs, NAVIGATOR and SOURCE, and one Phase 2 RCT, PATHWAY. The NAVIGATOR trial showed that at Week 52, tezepelumab reduced AAER by 56% (rate ratio [RR]: 0.44; 95% CI: 0.37, 0.53; p<0.001). The PATHWAY trial showed that, at Week 52, tezepelumab reduced AAER by 71% (RR: 0.29; 95% CI: 0.16,0.51; p<0.001). The SOURCE trial demonstrated that the cumulative odds of achieving a category of greater percentage reduction in OCS dose for daily maintenance at Week 48 with tezepelumab versus placebo were odds ratio [OR] of 1.28 (95% CI: 0.69, 2.3; p=0·43). (Results are contextualised in Section B.2.13.2.1).

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 experienced 3 or more exacerbations in the prior year, or who are on mOCS, irrespective of biomarker values, as outlined in Figure 5.

Figure 5: Proposed positioning of tezepelumab in the treatment pathway of 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.

B.1.4 Equality considerations

A recommendation for tezepelumab in patients with severe, uncontrolled asthma who have 3 or more exacerbations in the prior year OR who are on mOCS, as outlined in Section B.1.3.10, addresses existing inequality issues 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 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 (60). This is supported by the demographics in the tezepelumab NAVIGATOR trial (see Section B.2.3.3.2), 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) (106). 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.

B.2 Clinical effectiveness

SUMMARY

- The pivotal evidence for tezepelumab for the treatment of severe asthma comes from one Phase 2 RCT, PATHWAY (42, 107), and two Phase 3 RCTs, NAVIGATOR (43, 108, 109) and SOURCE (110)
- In PATHWAY and NAVIGATOR, tezepelumab treatment over 52 weeks resulted in clinically meaningful and statistically significant reductions in exacerbation rates of 71% and 56%, respectively, versus placebo (both p<0.001)
- In both studies, [redacted]
- Treatment with tezepelumab resulted in clinically meaningful reductions in AAER versus placebo irrespective of baseline EOS levels, FeNO levels, allergic status, and serum IgE
- Tezepelumab treatment was also shown to result in clinically meaningful improvements over 52 weeks in lung function (pre-BD FEV_1), quality of life (AQLQ(S)+12), asthma control (ACQ-6), and asthma symptoms (ASD) compared with placebo
- By preventing exacerbations, tezepelumab prevents patients from requiring either short bursts or chronic OCS use, reduces the need for OCS in OCS-dependent patients and demonstrates clinically meaningful improvements in key outcomes for OCS-dependent patients
- Although SOURCE did not meet its primary endpoint, it did demonstrate a numerical improvement in the odds of achieving a categorical reduction in mOCS dose with tezepelumab treatment versus placebo
- Tezepelumab 210 mg SC Q4W is well tolerated in adults and adolescents 12 years and older with severe asthma

B.2.1 Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix D.

A systematic literature review (SLRs) were conducted 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.

B.2.2 List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for tezepelumab for the treatment of patients with severe, uncontrolled asthma is provided in Table 6 (PATHWAY), Table 7 (NAVIGATOR), and Table 8 (SOURCE).

The primary references used for writing up each of the three pivotal trials are as follows:

- PATHWAY: Corren et al 2017 (42), Clinical Study Report (107)
- NAVIGATOR: Menzies-Gow et al 2020 (43), Menzies-Gow et al 2021 (109) Clinical Study Report (108)
- SOURCE: Clinical Study Report (110)

Table 6: Clinical effectiveness evidence – PATHWAY

Study (citations)	NCT02054130 (42, 107)				
Study design	Phase 2, multicentre, multinational, dose-ranging, double-blind, randomised, parallel-arm, placebo-controlled 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.				
Intervention(s)	In addition to standard of care: • Tezepelumab 70 mg SC Q4W • Tezepelumab 210 mg SC Q4W • Tezepelumab 280 mg SC Q2W				
Comparator(s)	Placebo SC Q2W (in addition to standard of care)				
Indicate if trial supports application for marketing authorisation	Yes	***X***	Indicate if trial used in the economic model	Yes	***X***†
	No			No	
Rationale for use/non-use in the model	Used in the economic model (indirectly via the NMA). PATHWAY provides relevant evidence for the efficacy and safety of tezepelumab used according to its (proposed) licensed dose for the treatment of patients with severe, uncontrolled asthma.				
Reported outcomes specified in the decision problem (outcomes marked in bold informed the model)	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) 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

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; $FEF_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NMA, network meta-analysis; OCS, oral corticosteroid; PEF, peak expiratory flow; PGI-C, Patient Global Impression of Change; 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.

Table 7: Clinical effectiveness evidence – NAVIGATOR

Study (citations)	NCT03347279 (43, 108, 109)				
Study design	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study				
Population	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.				
Intervention(s)	Tezepelumab 210 mg SC Q4W (in addition to standard of care)				
Comparator(s)	Placebo SC Q4W (in addition to standard of care)				
Indicate if trial supports application for marketing authorisation	Yes	***X***	Indicate if trial used in the economic model	Yes	***X***
	No			No	
Rationale for use/non-use in the model	Used in the economic model. NAVIGATOR provides relevant evidence for the efficacy and safety of tezepelumab used according to its (proposed) licensed dose for the treatment of patients with severe, uncontrolled asthma.				
Reported outcomes specified in the decision problem (outcomes marked in bold informed the model)	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 that require unscheduled contact with healthcare professionals or hospitalisation: • **AAER** (exacerbation = requiring SCS/OCS burst, ER visit, or hospitalisation) 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

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; $FEF_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; OCS, oral corticosteroid; PEF, peak expiratory flow; PGI-C, Patient Global Impression of Change; 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.

Table 8: Clinical effectiveness evidence – SOURCE

Study (citation)	NCT03406078 (110)				
Study design	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study				
Population	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, mOCS 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)	Tezepelumab 210 mg SC Q4W plus ICS/LABA and mOCS (in addition to standard of care)				
Comparator(s)	Placebo SC Q4W plus ICS/LABA and mOCS (in addition to standard of care)				
Indicate if trial supports application for marketing authorisation	Yes	***X***	Indicate if trial used in the economic model	Yes	***X***
	No			No	
Rationale for use/non-use in the model	Used in the economic model. SOURCE provides relevant evidence for the efficacy and safety of tezepelumab used according to its (proposed) licensed dose for the treatment of patients with severe, uncontrolled asthma as well as evidence for mOCS reduction.				
Reported outcomes specified in the decision problem	Asthma control: • **ACQ-6**, night-time awakenings requiring rescue medication Incidence of clinically significant exacerbations, including those that require 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 mOCS at Week 4** • **Proportion of subjects with daily mOCS dose ≤5 mg at Week 48** • **Proportion of subjections with ≥50% reduction from baseline in daily mOCS 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; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; ER, emergency room; $FEF_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; PEF, peak expiratory flow; 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.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Comparative summary of trial methodology

The methodologies of the pivotal Phase 2 RCT, PATHWAY, and that of its follow-on, pivotal Phase 3 RCT, NAVIGATOR, are summarised in Table 9.

The methodology of the pivotal Phase 3 RCT, SOURCE, is summarised in Table 10.

Table 9: Comparative summary of PATHWAY and NAVIGATOR methodology

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
Study objective	To evaluate the effect of three dose levels of tezepelumab SC (70 mg Q4W, 210 mg Q4W, 280 mg Q2W) on the annualised asthma exacerbation rate (AAER) in adult subjects with inadequately controlled, severe asthma	To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe, uncontrolled asthma compared with placebo
Trial design	Phase 2, multicentre, multinational, dose-ranging, double-blind, randomised, parallel-arm, placebo-controlled study (see Figure 6)	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study (see Figure 7)
Duration of study	The study consisted of a screening/run-in period of approximately 5 weeks, followed by a treatment period of 52 weeks, and a post-treatment follow-up period of 12 weeks (see Figure 6)	The study consisted of a screening/run-in period between 5 and 6 weeks, a treatment period of 52 weeks, and a post-treatment follow-up period of 12 weeks (see Figure 7)
Method of randomisation	Randomisation (1:1:1:1) was achieved via an IWRS. Prior to randomisation, all subjects were stratified by study site (non-Japanese and Japanese), and then blood EOS count (≥ or <250 cells/μL) and by ICS dose level (medium or high).	Randomisation (1:1) was achieved via an IWRS with subject randomisation codes grouped in blocks. All subjects were stratified at randomisation by age group (adults versus adolescents) and region.
Method of blinding (care provider, patient and outcome assessor)	Since tezepelumab and placebo were not identical, an unblinded investigational product manager prepared the investigational product. Once the investigational product was in the dosing syringes, tezepelumab and placebo were indistinguishable, so the investigational product was administered by a blinded study team member. An unblinded investigational product monitor performed investigational product accountability. In the event that treatment allocation for a subject became known to the investigator or other study staff involved in the management of study subjects, the sponsor was required to be notified immediately. The site maintained a written plan detailing which staff members were blinded/unblinded and the process of investigational product administration used to maintain the blind. To ensure the blinding of each subject's treatment assignment throughout the study, both the interim analysis and the Stage I analysis were performed by a limited number of sponsor personnel who were not directly involved in the conduct of the study. Study site personnel, sponsor personnel directly associated with the conduct of this study, and subjects remained blinded	All packaging and labelling of investigational products was done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the subject nor any of the investigators or sponsor staff involved in the treatment or clinical evaluation and monitoring of the subjects was aware of the treatment received. Since tezepelumab and placebo were not visually distinct, investigational products were handled by a qualified person (e.g. pharmacist or study nurse) at the site. No member of the extended study team had access to the randomisation scheme during the conduct of the study until after the primary database lock.

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
	to the treatment assignment for individual subjects until the completion of the study.	
Eligibility criteria for participants	(The full inclusion and exclusion criteria are provided in Appendix L) • Aged 18–75 years (inclusive) • Physician-diagnosed asthma for ≥12 months prior to Visit 1 • Physician-prescribed asthma controller regimen with medium- or high-dose ICS plus LABA for ≥6 months prior to Visit 1 • ACQ-6 score ≥1.5 at screening • ≥2 asthma exacerbation events or ≥1 severe asthma exacerbation resulting in hospitalisation within 12 months prior to Visit 1	(The full inclusion and exclusion criteria are provided in Appendix M) • Aged 12–80 years (inclusive) • Physician-diagnosed asthma for ≥12 months prior to Visit 1 • Documented treatment with a total daily dose of either medium- or high-dose ICS for ≥3 months prior to Visit 1 • Use of additional asthma controller medications for ≥3 months prior to Visit 1 • ACQ-6 score ≥1.5 at screening • ≥2 asthma exacerbation events within 12 months prior to Visit 1
Settings and locations where the data were collected	Subjects were enrolled in 98 centres in 12 countries (Bulgaria, Czech Republic, Hungary, Israel, Japan, Latvia, Lithuania, Serbia, Slovakia, South Africa, Ukraine, United States)	Subjects were enrolled at 297 centres in 18 countries (Argentina, Australia, Austria, Brazil, Canada, France, Germany, Israel, Japan, South Korea, Russia, Saudi Arabia, South Africa, Taiwan, Ukraine, United Kingdom, United States, and Vietnam)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	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) • Placebo SC Q2W (n=138)	• Tezepelumab 210 mg SC Q4W in addition to standard of care (n=528) • Placebo SC Q4W in addition to standard of care (n=531)
Permitted and disallowed concomitant medications	Permitted concomitant medications: If the subject was taking additional asthma controller medications (including leukotriene modifiers, theophylline, cromones, or mOCS [up to a maximum of prednisone 10 mg daily or 20 mg every other day; or equivalent]), then these medications were continued at a stable dose during the screening/run-in period and to Week 64. Subjects who were taking theophylline were monitored appropriately by the	Use of the following concomitant medications was permitted and documented: • All ICS asthma medications taken in the 12 months prior to Visit 1 • A history of continuous treatment with medium or high dose ICS plus a second controller medication for ≥3 months prior to Visit 1

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
	investigator during the conduct of this study. During the study, subjects may have used an inhaled short-acting bronchodilator or an inhaled short-acting anticholinergic on an as-required basis as a reliever or rescue medication. Investigators may have prescribed any other concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded". The following concomitant medications related to asthma/allergy treatment were also permitted from screening through Week 64: • Mucolytics and expectorants not containing bronchodilators. • Maintenance regimen of allergen-specific immunotherapy was allowed but should not have been administered on the same day as the investigational product. Subjects should have commenced the regimen for at least 2 months prior to Visit 1 and should have remained on a maintenance regimen throughout the study • Topical, nasal, and/or ocular formulations of corticosteroids or cromones • Topical or oral antihistamines • Inactivated vaccines Excluded concomitant medications: The following medications were considered exclusionary and were not permitted during the study. The sponsor was to be notified if a subject received any of these during the study: • Immunosuppressive medication (e.g. methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid) • OCS for chronic use in diseases other than asthma; short bursts (≤7 days) of SCS for other acute inflammatory diseases were permitted • 5-lipoxygenase inhibitors (zileuton) • Investigational agents other than tezepelumab • Marketed biologics including omalizumab	• All asthma controller medications for the 3 months prior to Visit 1 until the end of the study • All other medications taken for conditions other than asthma in the 3 months prior to Visit 1 Subjects on maintenance treatment with theophylline were required to have blood concentration levels within therapeutic range, documented before Visit 1 Restricted medications: The following medications were not permitted from Visit 1 and throughout the treatment period, and preferably not until 4 weeks after the last dose of investigational product: • Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations) • SABAs • Additional maintenance controllers • Short-acting anticholinergics (e.g. ipratropium), except for managing an asthma exacerbation event Inactive/killed vaccinations were permitted provided they were administered within 5 days before or after any study visit. Allergen immunotherapy was allowed if on stable therapy for ≥2 months prior to Visit 1 with no changes to treatment anticipated. Prohibited medications: LABAs as a reliever, Suplatast tosilate, live attenuated vaccines, any immunomodulators or immunosuppressives (except OCS used in maintenance treatment of asthma, asthma exacerbations in screening/run-in, and protocol-defined asthma exacerbations on or after Visit 3), immunoglobulin or blood products, any investigational biologic treatment, any other investigational products, herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases, medications not currently licensed for use in the treatment of asthma, e.g. medications approved for COPD and not part of standard of care.

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
	• Immunoglobulin or blood products • Use of any oral or ophthalmic β-adrenergic antagonist (e.g. propranolol) • Live or attenuated vaccines • Subjects were not to begin allergen-specific immunotherapy from 2 months before Visit 1 through Week 64 • Th2 cytokine inhibitor (suplatast)	Rescue medication use: SABA was to be withheld for ≥6 hours prior to scheduled site visit spirometry, FeNO, ECG at site with the exception of any unscheduled visits due to asthma worsening. Regularly scheduled SABA use in the absence of any asthma symptoms was not allowed from enrolment (Visit 1) and for the remainder of the study duration. Prophylactic use of SABA, or any other use than to curb worsening of asthma symptoms, was to be documented. Rescue use of SABA administered via nebulisation was to be discouraged, except as urgent treatment during an asthma exacerbation, in which case its use was to be documented.
Primary outcome (including scoring methods and timings of assessments)	Annualised asthma exacerbation rate (AAER) measured at Week 52 To qualify as an asthma exacerbation the event must have required: • Administration of a burst of SCS for at least 3 consecutive days, or • An ER visit, which required SCS for at least 3 consecutive days or hospitalisation. For subjects receiving mOCS, a temporary doubling of the stable existing maintenance dose for at least 3 days qualified	Annualised asthma exacerbation rate ratio (AAER) measured at Week 52 An asthma exacerbation was defined as a worsening of asthma that led to any of the following: • A temporary bolus/burst of SCS (or a temporary increase in stable mOCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening. • An ER 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.
Key secondary/other outcomes used in the economic model/specified in the scope	• Reduction in AER • CFB in FEV_1 • CFB in overall symptom score • CFB in lung function (pre-BD FEV_1, post-BD FEV_1, FVC) • CFB in asthma symptoms (day-time and night-time symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue, rescue	• CFB in pre-BD FEV_1 • CFB in AQLQ(S)+12 • CFB in ACQ-6 • CFB in weekly mean daily Asthma Symptom Diary score • Time to first asthma exacerbation • Proportion of subjects experiencing no asthma exacerbations over 52 weeks

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
	medication use) as measured by Asthma Daily Diary and ACQ-6 • Annualised rate of hospitalisations due to asthma • Time to first asthma exacerbation/severe asthma exacerbation, and proportion of subjects with one or more asthma exacerbations/severe asthma exacerbations at Week 52 • CFB in AQLQ(S)+12 • CFB in EQ-5D-5L • CFB in WPAI+CIQ • AEs	• Annualised rate of exacerbations associated with ER visit or hospitalisation • CFB in FeNO (ppb) • CFB in peripheral blood eosinophils • CFB in total serum IgE • CFB in weekly mean rescue medication use • CFB in weekly mean morning and evening PEF CFB in weekly mean number of night-time awakenings • Asthma-specific resource utilisations (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • CFB in WPAI+CIQ • CFB in EQ-5D-5L • CFB in PGI-C, PGI-S, and CGI-C • CFB in post-BD FEV_1 and $FEF_{25–75\%}$ • Change over time in FeNO, pre-BD FEV_1, ACQ-6, asthma symptoms, and rescue medication use • CFB in SGRQ • AEs
Pre-planned subgroups	AAER, FEV_1, ACQ-6, AQLQ, and overall symptom score at Week 52 were analysed in the following pre-specified subgroups: • Baseline EOS: – ≥250 cells/μL, <250 cells/μL • Th2 high/low: – IgE >100 IU/mL AND EOS count ≥140 cells/μL, IgE ≤100 IU/mL OR EOS <140 cells/μL • FeNO high/low: – ≥median versus <median • Periostin high/low: – ≥median versus <median)	Descriptive summaries of AAER were presented for the following pre-specified subgroups: • Baseline EOS: – <300 cells/μL, ≥300 cells/μL – <150 cells/μL, 150 to <300 cells/μL, 300 to <450 cells/μL, ≥450 cells/μL – <150 cells/μL, ≥150 cells/μL • Baseline clinic visit FeNO: – 25 ppb, ≥25 ppb – <25 ppb, 25 to <50 ppb, ≥50 ppb

	NCT02054130 (PATHWAY)	NCT03347279 (NAVIGATOR)
	• Current post-BD FEV_1 reversibility: – Post-BD change in FEV_1 of ≥12% and ≥200 mL at one of the screening visits • Allergic and non-allergic asthma: allergic if any of specific IgE panel items was positive in FEIA IgE data • Study sites: non-Japanese versus Japanese • ICS dose level: medium versus high • No chronic OCS use and current post-BD FEV_1 reversibility In addition, a non-pre-specified EOS cut-off of ≥300 cells/μL versus <300 cells/μL was used for subgroup analysis of the primary efficacy endpoint.	• Baseline perennial aeroallergen-specific IgE status: any perennial FEIA positive, all perennial FEIA negative, unknown perennial FEIA Additional descriptive analyses were provided for the following exploratory subgroups: • ICS dose at study entry: medium, high • Age category used for stratification: adults (≥18 years) and adolescents (≥12 to <18 years) • Age category: adults (≥65 years), adults (≥18 to <65 years), and adolescents (≥12 to <18 years) • Gender • Race • Exacerbations in the year before study: ≤2, >2 • OCS at baseline: present, absent • BMI • Geographical region • Nasal polyps in the 2 years before randomisation: yes, no • Biomarker quartiles • Weight quartiles • Drug concentration exposure quartiles

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AE, adverse event; AER, asthma exacerbation rate; AQLQ, Asthma Quality of Life Questionnaire; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; BD, bronchodilator; BMI, body mass index; CFB, change from baseline; CGI-I, Clinician Global Impression of Change; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EOS, eosinophil; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; ER, emergency room; $FEF_{25–75\%}$, forced expiratory flow over 25–75% of the vital capacity; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; IU, International Unit; IWRS, Interactive Web Response System; LABA, long-acting beta agonist; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; PEF, peak expiratory flow; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SABA, short-acting beta agonist; SC, subcutaneous; SCS, systemic corticosteroid; SGRQ, St George's Respiratory Questionnaire; WPAI-CIQ, Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire.

Table 10: Summary of SOURCE methodology

	NCT03406078 (SOURCE)
Study objective	To evaluate the effect of a 210 mg dose of tezepelumab SC Q4W on mOCS dose reduction in adult subjects with severe, mOCS-dependent asthma
Trial design	Phase 3 multicentre, global, randomised, double-blind, placebo-controlled, parallel group study (see Figure 8)
Duration of study	The study consisted of a 2-week screening/run-in period followed by an mOCS optimisation phase of up to 8 weeks, a treatment period of 48 weeks (comprising a 4-week induction phase, a 36-week mOCS reduction phase, and an 8-week maintenance phase), and a post-treatment follow-up period of 12 weeks (see Figure 8)
Method of randomisation	Randomisation (1:1) was achieved via an IWRS with subject randomisation codes grouped in blocks. All subjects were stratified at randomisation by region.
Method of blinding (care provider, patient and outcome assessor)-	Tezepelumab and placebo were not visually distinct from each other. All packaging and labelling of investigational products was done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the subject nor any of the investigators or sponsor staff who were involved in the treatment or clinical evaluation and monitoring of the subjects were aware of the treatment received. To further prevent unblinding, blood eosinophil, basophils and monocyte numbers from the visits after randomisation visit were redacted from the central laboratory reports. In addition, FeNO results were blinded throughout the study.
Eligibility criteria for participants	(The full inclusion and exclusion criteria are provided in Appendix N) • Aged 18–80 (inclusive) • Physician-diagnosed asthma for ≥12 months prior to Visit 1 • Physician-prescribed medium- or high-dose ICS as per GINA guidelines for ≥12 months prior to Visit 1 • Physician-prescribed LABA and high-dose ICS for ≥3 months prior to Visit 1 • 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 prior to Visit 1
Settings and locations where the data were collected	Subjects were enrolled at 60 centres in 7 countries (Argentina, Germany, South Korea, Turkey, Poland, Ukraine, and USA)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	In addition to standard of care: • Tezepelumab 210 mg SC Q4W plus ICS/LABA and mOCS (n=74) • Placebo SC Q4W plus ICS/LABA and mOCS (n=76)
Permitted and disallowed concomitant medications	Use of the following concomitant medications was permitted and documented: • Physician-prescribed medium- or high-dose ICS as per GINA guidelines for ≥12 months prior to Visit 1 • Physician-prescribed LABA and high-dose ICS (total daily dose >500 µg fluticasone propionate dry powder formulation equivalent) for ≥3 months prior to Visit 1

	NCT03406078 (SOURCE)
	• Additional maintenance asthma controller medications according to standard practice of care; use of these medications must have been documented for ≥3 months prior to Visit 1 • mOCS for the treatment of asthma for ≥6 months prior to Visit 1 and a stable dose of between ≥7.5 mg to ≤30 mg (prednisone or prednisolone) daily or daily equivalent for ≥1 month prior to Visit 1 Subjects who were maintained on LAMA, theophylline, or LTRA were required to continue treatment with these medications throughout the study. Restricted medications: The following medications were not permitted from Visit 1, throughout the treatment period, and preferably not until 4 weeks after the last dose of investigational product: • Maintenance treatment with long-acting bronchodilators (including ICS/LABA combinations) • SABAs (regular, scheduled use; prn use was permitted with restrictions) • Additional maintenance controllers • Short-acting anticholinergics (e.g., ipratropium), except for managing an asthma exacerbation event Inactive/killed vaccinations were permitted provided they were administered within 5 days before or after any study visit. Allergen immunotherapy was allowed if on stable therapy for ≥30 days prior to Visit 1 with no anticipated change during treatment period Prohibited medications: LABAs as a reliever; suplatast tosilate; any immunomodulators or immunosuppressives (corticosteroids with systemic effects such as oral, parenteral, or intra-articular administration for reasons other than asthma were not allowed; however, corticosteroid treatment of adrenal insufficiency and acute anaphylaxis was allowed); immunoglobulin or blood products; any marketed or investigational biologic treatment; other investigational product; herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases; medications not currently licensed for use in the treatment of asthma, e.g., medications approved for COPD and not part of standard of care; live attenuated vaccines; spironolactone; eplerenone; ephedrine; opiates. Rescue mediation use: SABA was to be withheld for ≥6 hours prior to scheduled site visit spirometry, FeNO, ECG tests and home lung function assessments with the exception of any unscheduled visits due to asthma worsening. Regularly scheduled SABA use in the absence of any asthma symptoms was not allowed from enrolment (Visit 1) and for the remainder of the study duration. Prophylactic use of SABA, or any other use than to curb worsening of asthma symptoms, was to be documented. Rescue use of SABA administered via nebulisation was to be discouraged, except as treatment during an asthma exacerbation, in which case its use was to be documented.
Primary outcome (including scoring methods and timings of assessments)	Categorised percent reduction from baseline in the daily OCS at Week 48 while not losing asthma control.† The categories for percent change from baseline in daily OCS dose were defined as: • ≥90% to ≤100% reduction • ≥75% to <90% reduction • ≥50% to <75% reduction • >0% to <50% reduction • No change or any increase

	NCT03406078 (SOURCE)
Other outcomes used in the economic model/specified in the scope	• AAER • Time to first asthma exacerbation • Rate of asthma exacerbation associated with ER visit, urgent care visit, or hospitalisation • Proportion of subjects who did not experience an asthma exacerbation • Proportion of subjects with 100% reduction from baseline 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 • CFB in pre-BD FEV_1 • CFB in weekly mean daily Asthma Symptom Diary Score as captured in the daily Asthma Symptoms Diary (ASD) • CFB in weekly mean rescue medication use • CFB in weekly mean home PEF (morning and evening) • CFB in weekly mean number of night-time awakenings due to asthma • CFB in ACQ-6 • CFB in AQLQ(S)+12 • CFB in EQ-5D-5L • Number of asthma-specific resource utilisations (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • CFB in WPAI+CIQ score • CFB in SGRQ • CFB in FeNO, peripheral blood eosinophils, and total IgE • AEs
Pre-planned subgroups	The following subgroups were defined for the purposes of efficacy subgroup analysis and/or baseline summaries: • Baseline EOS – <300 cells/µL, ≥300 cells/µL – <150 cells/µL, ≥150 cells/µL • *Baseline clinic visit FeNO: – <25 ppb, ≥25 ppb • Baseline clinic visit FeNO: – <25 ppb – ≥25 to <50 ppb – ≥50 ppb • Baseline IgE status: allergic, non-allergic (defined by a positive IgE result specific to any perennial aeroallergen in the FEIA panel versus negative results for all perennial aeroallergens in the panel) • Daily OCS dose at randomisation (≤10 mg versus >10 mg prednisone or prednisolone) • Age category: aged ≥18 to ≤65, aged ≥65 • Gender • Race • BMI • Geographical region

	NCT03406078 (SOURCE)
	• Country

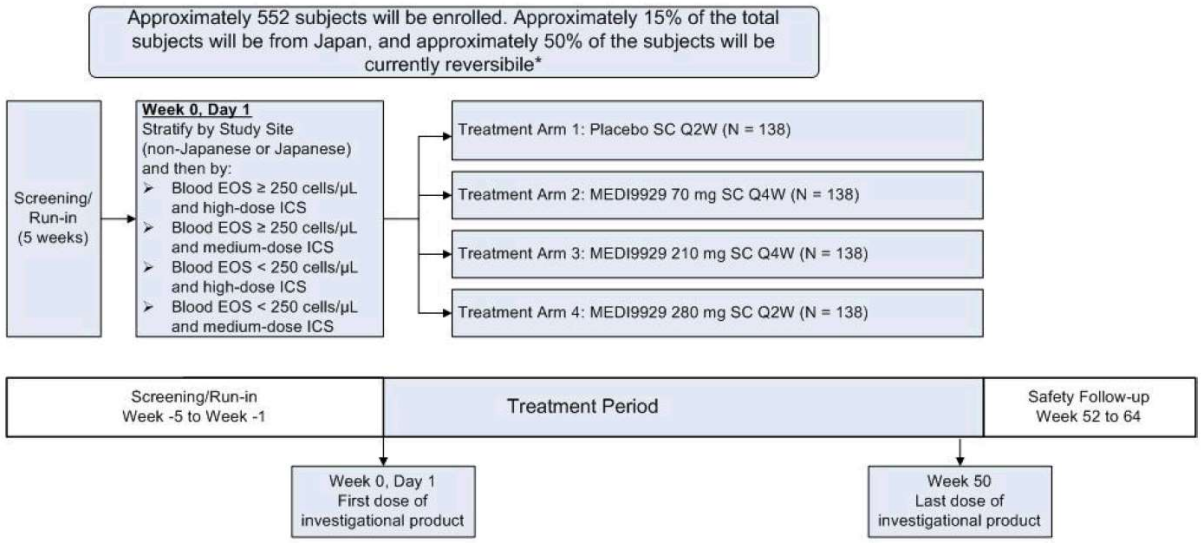
Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AE, adverse event; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; BMI, body mass index; CFB, change from baseline; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EOS, eosinophil; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; ER, emergency room; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; IWRS, Interactive Web Response System; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PEF, peak expiratory flow; ppb, parts per billion; Q4W, once every 4 weeks; SABA, short-acting beta agonist; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire; Th, T helper cell; WPAI+CIQ, Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire.
† Repeated attempts at OCS reduction were permitted. If a subject could not reduce OCS because of loss of asthma control, they could try again at a later visit after control was regained.

B.2.3.2 Trial design schematics

Schematics illustrating the trial designs of PATHWAY, NAVIGATOR, and SOURCE are provided in Sections B.2.3.2.1, B.2.3.2.2, and B.2.3.2.3, respectively.

B.2.3.2.1 PATHWAY

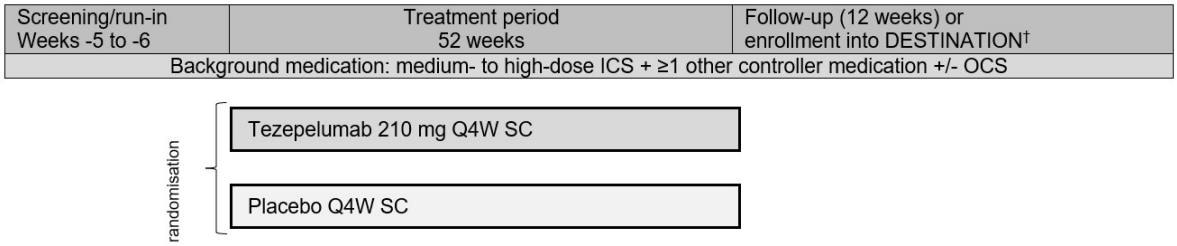
Figure 6: Schematic of PATHWAY trial design



Abbreviations: EOS, eosinophil; ICS, inhaled corticosteroid; MEDI9929, tezepelumab; Q4W, once every 4 weeks; SC, subcutaneous.
* Current post-BD FEV_1 reversibility was defined as post-BD change in FEV_1 of ≥12% and ≥200 mL at one of the screening visits.

B.2.3.2.2 NAVIGATOR

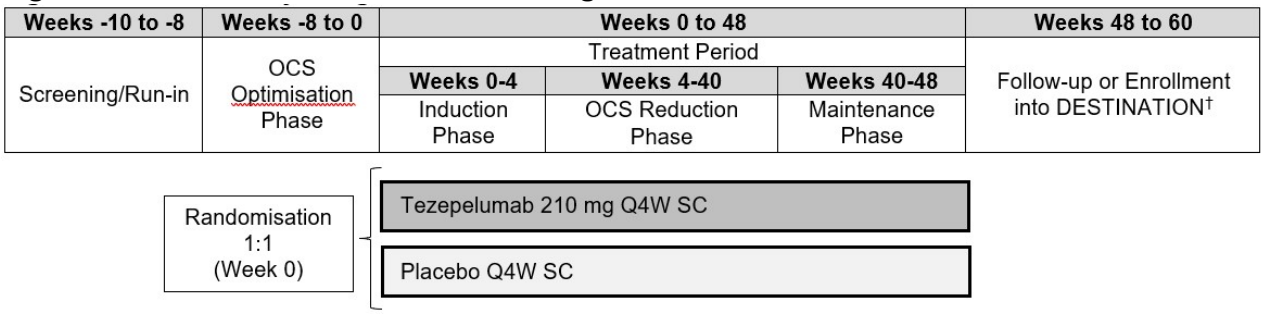
Figure 7: Schematic of NAVIGATOR trial design



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

B.2.3.2.3 SOURCE

Figure 8: 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.

B.2.3.3 Baseline characteristics and demographics

B.2.3.3.1 PATHWAY

Baseline demographic, clinical characteristics, and asthma history of subjects enrolled in PATHWAY are summarised in Table 11, Table 12, and Table 13, respectively.

Subject demographic and clinical characteristics were generally well balanced between the tezepelumab and placebo trial arms. Overall, the study population represented the intended population of severe, uncontrolled asthma.

The majority of subjects in the intent-to-treat (ITT) population (see Section B.2.4.2 for definitions of analysis sets) were white (91.6%), female (65.6%), and not Hispanic or Latino ([redacted] The mean age was 51.55 years (range: 20–75 years), and the average body mass index (BMI) was 28.20 (Table 11).

In terms of asthma characteristics at baseline, overall:

- [redacted] of subjects in the tezepelumab (any dose) and placebo arms, respectively, were receiving mOCS at baseline
- [redacted] of subjects in the tezepelumab (any dose) and placebo arms, respectively, had positive aeroallergen-specific IgE status (fluorescent enzyme immunoassay [FEIA])
- [redacted] of subjects in the tezepelumab (any dose) and placebo arms, respectively, had experienced ≥2 exacerbations in the prior 12 months
- [redacted] of subjects in the tezepelumab (any dose) and placebo arms, respectively, had experienced ≥3 exacerbations in the prior 12 months
- [redacted] of subjects in the tezepelumab (any dose) and placebo arms, respectively, had experienced ≥4 exacerbations in the prior 12 months

Table 11: PATHWAY baseline demographic characteristics (ITT)

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)	Total (N=550)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)		
Age, years						
Mean (SD)	50.80 (12.36)	52.66 (12.67)	50.43 (12.25)	51.30 (12.43)	52.32 (11.71)	51.55 (12.25)
Min, Max	20, 74	21, 75	21, 72	20, 75	20, 74	20, 75
Sex, n (%)						
Male	49 (35.5)	50 (36.5)	46 (33.6)	145 (35.2)	44 (31.9)	189 (34.4)
Female	89 (64.5)	87 (63.5)	91 (66.4)	267 (64.8)	94 (68.1)	361 (65.6)
Ethnicity, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)†						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple categories checked	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2						
Mean (SD)	28.30 (5.05)	28.50 (4.91)	27.56 (5.00)	28.12 (4.99)	28.45 (5.55)	28.20 (5.14)
Min, Max	18.5, 39.8	19.8, 39.5	18.3, 39.5	18.0, 39.8	18.0, 44.4	18.0, 44.4

Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, standard deviation.
† Each race category counted subjects who selected only that category. “Multiple categories checked” counted subjects who selected more than one race category.

Table 12: PATHWAY baseline disease characteristics (ITT)

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
Blood EOS count, n (%)					
≥250 cells/μL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<250 cells/μL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS level, n (%)					
Medium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study site, n (%)					
Non-Japanese	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Japanese	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance OCS use, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-BD FEV_1, L					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-BD FEV_1, % predicted					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-BD FEV_1 reversibility, %					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of asthma exacerbations in the past 12 months, n (%)					
1 or 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACQ-6					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
Overall AQLQ(S)+12					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall Asthma Symptom Score					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central blood EOS count, cells/µL					
≥300, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<300, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Th2 Status, n (%)					
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Serum IgE, IU/mL					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FeNO, ppb					
≥24, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<24, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic asthma status, n (%)					
Allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical Region, n (%)					

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
North America/Western EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of world	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; BD, bronchodilator; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; ITT, intent-to-treat, IU, International Unit; OCS, oral corticosteroid; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, standard deviation; Th, T helper cell.

Table 13: PATHWAY baseline asthma history (ITT)

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)	Total (N=550)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)		
Childhood asthma, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age of onset, childhood asthma						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age of adult asthma onset						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Family history: parents, n (%)						

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)	Total (N=550)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)		
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Family history: siblings, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation history: number of exacerbations in the past 12 months, n (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Night-time awakenings (last 3 months), n (%)						
0–1/month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3–4/month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>2/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)	Total (N=550)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)		
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SABA use (last 3 months), n (%)						
0–2 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3–6 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough, wheeze, shortness of breath, chest tightness (last 3 months), n (%)						
0–2 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3–6 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 days/week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interference with normal activity (last 3 months), n (%)						
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS bursts, last 3 months						
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS use, n (%)						
Subjects using ≥1 ICS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budesonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluticasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NCT02054130 (PATHWAY) Baseline characteristics	Tezepelumab				Placebo Q2W (n=138)	Total (N=550)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)		
Fluticasone propionate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Beclometasone dipropionate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Beclometasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Fluticasone furoate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Mometasone furoate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Ciclesonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Mometasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
mOCS use, n (%)						
Subjects using ≥1 OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Triamcinolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR

Abbreviations: ICS, inhaled corticosteroid; ITT, intent-to-treat, max, maximum; min, minimum; mOCS, maintenance oral corticosteroid treatment; NA, not applicable; OCS, oral corticosteroid; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SABA, short-acting beta agonist; SD, standard deviation.

B.2.3.3.2 NAVIGATOR

Baseline demographic and clinical characteristics of subjects enrolled in NAVIGATOR are summarised in Table 14 and Table 15, respectively. (Additional baseline characteristics of lesser importance are presented in Appendix M).

Subject demographic and clinical characteristics were generally balanced between the tezepelumab and placebo trial arms. Overall, the study population represented the intended population of severe, uncontrolled asthma.

The majority of subjects in the full analysis set (FAS) (see Section B.2.4.2 for definitions of analysis sets) were white (62.2%), female (63.5%), and not Hispanic or Latino (84.5%). The mean age was 49.5 years (range: 12–80 years), and the average BMI was 28.49. A total of 82 subjects were aged ≥12 to 17 years (i.e. adolescents [7.7%]) and the remaining subjects were adults, 170 of whom (16.1%) were aged ≥65 to 80 years (Table 14).

In terms of asthma characteristics at baseline, overall:

- 9.4% of subjects were receiving mOCS at baseline
- 58.4% of subjects had EOS<150 cells/μL and 41.6% had EOS ≥300 cells/μL
- 68.5% of subjects had positive aeroallergen-specific IgE status (FEIA)
- 99.9% of subjects had experienced ≥2 exacerbations in the prior 12 months
- 40.0% of subjects had experienced ≥3 exacerbations in the prior 12 months
- 16.8% of subjects had experienced ≥4 exacerbations in the prior 12 months.

Table 14: NAVIGATOR baseline demographic characteristics (FAS)

NCT03347279 (NAVIGATOR) Baseline† characteristics	Tezepelumab (n=528)	Placebo (n=531)	Total (N=1,059)
Age, years			
Mean (SD)	49.9 (16.3)	49.0 (15.9)	49.5 (16.1)
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Age group, n (%)			
Adolescent (≥12 to <18 years)	[redacted]	[redacted]	[redacted]
Adult (≥18 to <65 years)	[redacted]	[redacted]	[redacted]
Adult (≥65 years)	[redacted]	[redacted]	[redacted]
Adult (≥18 years)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	193 (36.6)	194 (36.5)	387 (36.5)
Female	335 (63.4)	337 (63.5)	672 (63.5)

NCT03347279 (NAVIGATOR) Baseline† characteristics	Tezepelumab (n=528)	Placebo (n=531)	Total (N=1,059)
Race, n (%)			
White	332 (62.9)	327 (61.6)	659 (62.2)
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
BMI, kg/m^2			
Mean (SD)	28.69 (7.09)	28.30 (6.89)	28.49 (6.99)
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; FAS, full analysis set; max, maximum; min, minimum; SD, standard deviation.
† Baseline was defined as the last non-missing measurement recorded on or prior to randomisation.

Table 15: NAVIGATOR baseline clinical characteristics (FAS)

NCT03347279 (NAVIGATOR) Baseline† characteristics	Tezepelumab (n=528)	Placebo (n=531)	Total (N=1,059)
EOS, cells/µL			
n	528	531	1,059
Mean (SD)	326.74 (293.33)	353.39 (488.40)	340.10 (403.15)
Median	250.00	250.00	250.00
Min, Max	[redacted]	[redacted]	[redacted]
EOS group, n (%)			
<150 cells/µL	[redacted]	[redacted]	[redacted]
150 to <300 cells/µL	[redacted]	[redacted]	[redacted]
300 to <450 cells/µL	[redacted]	[redacted]	[redacted]
≥450 cells/µL	[redacted]	[redacted]	[redacted]
FeNO, ppb			
n	522	527	1,049
Mean (SD)	41.38 (36.30)	46.27 (44.73)	43.83 (40.81)
Median	31.00	30.00	30.00
Min, Max	5.0, 235.0	5.0, 265.0	5.0, 265.0
FeNO group, n (%)			
<25 ppb	213 (40.8)	220 (41.7)	433 (41.3)

NCT03347279 (NAVIGATOR) Baseline† characteristics	Tezepelumab (n=528)	Placebo (n=531)	Total (N=1,059)
25 to <50 ppb	[redacted]	[redacted]	[redacted]
≥50 ppb	[redacted]	[redacted]	[redacted]
Number of exacerbations in the past 12 months, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]
Total IgE, IU/mL			
n	528	531	1,059
Mean (SD)	515.68 (959.75)	614.05 (1159.49)	565.00 (1065.23)
Median	194.85	196.70	195.60
Min, Max	[redacted]	[redacted]	[redacted]
Aeroallergen-specific IgE status (FEIA), n (%)			
Any FEIA positive	[redacted]	[redacted]	[redacted]
All FEIA negative	[redacted]	[redacted]	[redacted]
Unknown FEIA	[redacted]	[redacted]	[redacted]
Time since asthma diagnosis, years‡			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Time since asthma symptoms started, years‡			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Nasal polyps in the past 24 months, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
FEV_1 pre-BD, L			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
FEV_1 pre-BD, % PN			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

NCT03347279 (NAVIGATOR) Baseline† characteristics	Tezepelumab (n=528)	Placebo (n=531)	Total (N=1,059)
Median	[redacted]	[redacted]	[redacted]
Min, Max	18, 106	5, 127	15, 127
Reversibility in FEV_1, L§			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Reversibility in FEV_1, %§			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
AQLQ(S)+12 total score¶			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
ACQ-6 score at baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Weekly mean daily ASD score††			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
ICS dose group, n (%)			
Low	[redacted]	[redacted]	[redacted]
Medium	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]
Taking OCS, n (%)			
Yes	49 (9.3)	51 (9.6)	100 (9.4)
No	479 (90.7)	480 (90.4)	959 (90.6)

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; EOS, eosinophil; FAS, full analysis set; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IU, International Unit; max, maximum; min, minimum; OCS, oral corticosteroid; PN, predicted normal; ppb, parts per billion; SD, standard deviation.
† Baseline was defined as the last non-missing measurement recorded on or prior to randomisation.

‡ Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.
§ Reversibility in FEV_1 (L) was calculated as post-BD FEV_1 (L) – pre-BD FEV_1 (L). Reversibility in FEV_1 (%) was calculated as (post-BD FEV_1 (L) – pre-BD FEV_1 (L)) / pre-BD FEV_1 (L) × 100%. Current post-BD reversibility was defined as FEV_1 ≥12% and ≥200 mL during screening (15–30 mins after administration of four puffs of albuterol/salbutamol). If both Visit 2 and Visit 2a values were available, the highest of the reversibility values, i.e. the largest difference (post-BD FEV_1 – pre-BD FEV1) across the two visits was used to determine 'Yes' and 'No.' Inclusion into the study was based on current post-BD FEV_1 reversibility or on documented historical reversibility.
¶ ACQLQ(S)+12 was defined as the unweighted mean of the responses to all questions in the questionnaire. ACQ-6 score was defined as the unweighted mean of the responses to six questions. If responses to any of the ACQLQ(S)+12 or ACQ-6 questions were missing, the total score for the tool was considered missing. If more than 3 days were missing within a week, the weekly mean was set to missing. No imputation was made for missing values.
†† Daily ASD score was defined as the mean of the 10 items recorded in the evening (five items) and the following morning (five items).

B.2.3.3.3 SOURCE

Baseline demographic and clinical characteristics of subjects enrolled in SOURCE are summarised in Table 16 and Table 17, respectively. (Additional baseline characteristics of lesser importance are presented in Appendix N).

The majority of subjects in the FAS (see Section B.2.4.2 for definitions of analysis sets) were White (84.0%), female (62.7%), [redacted] The mean age was 53.4 years (range 22–76 years) and the mean BMI was 29.37. All patients were aged ≥18 years and 20.0% were aged ≥65 years.

Overall, the study population represented the intended population of adults with severe, mOCS-dependent asthma, and characteristics were generally well balanced between trial arms.

[redacted]

In terms of asthma characteristics at baseline, overall:

- 100% of subjects were receiving mOCS at baseline
- [redacted]

Table 16: SOURCE baseline demographic characteristics (FAS)

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
Age, years			
n	74	76	150
Mean (SD)	53.5 (12.1)	53.4 (11.9)	53.4 (12.0)
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Age group, n (%)			
Adult (≥18 to <65 years)	[redacted]	[redacted]	[redacted]
Adult (≥65 years)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	25 (33.8)	31 (40.8)	56 (37.3)
Female	49 (66.2)	45 (59.2)	94 (62.7)
Race, n (%)			
White	62 (83.8)	64 (84.2)	126 (84.0)
Black or African American	1 (1.4)	0 (0.0)	1 (0.7)
Asian	11 (14.9)	11 (14.5)	22 (14.7)
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ethnic group, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
BMI, kg/m^2			
n	74	76	150
Mean (SD)	29.29 (6.67)	29.44 (7.44)	29.37 (7.04)
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; FAS, full analysis set; max, maximum; min, minimum; SD, standard deviation.
† Baseline was defined as the last non-missing measurement recorded on or prior to randomisation.

Table 17: SOURCE baseline clinical characteristics (FAS)

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
EOS, cells/µL			
n	74	76	150
Mean (SD)	253.25 (203.12)	231.84 (153.81)	242.40 (179.55)
Median	215.00	200.00	200.00

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
Min, Max	[redacted]	[redacted]	[redacted]
EOS group (cells/µL), n (%)			
<150	27 (36.5)	24 (31.6)	51 (34.0)
150 to <300	19 (25.7)	28 (36.8)	47 (31.3)
300 to <450	[redacted]	[redacted]	[redacted]
≥450	[redacted]	[redacted]	[redacted]
FeNO (ppb)			
n	68	69	137
Mean (SD)	38.71 (40.82)	42.35 (37.44)	40.54 (39.05)
Median	26.00	28.00	27.00
Min, Max	[redacted]	[redacted]	[redacted]
FeNO group (ppb), n (%)			
<25	32 (47.1)	26 (37.7)	58 (42.3)
25 to <50	[redacted]	[redacted]	[redacted]
≥50	[redacted]	[redacted]	[redacted]
Total IgE (IU/mL)			
n	73	76	149
Mean (SD)	298.71 (576.28)	300.89 (521.39)	299.82 (547.10)
Median	109.40	122.65	109.70
Min, Max	[redacted]	[redacted]	
Aeroallergen-specific IgE status (FEIA), n (%)			
Any FEIA positive	[redacted]	[redacted]	[redacted]
All FEIA negative	[redacted]	[redacted]	[redacted]
Unknown FEIA	[redacted]	[redacted]	[redacted]
FEV_1 pre-BD, L			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
FEV_1 pre-BD, % PN			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
$FEF_{25–75\%}$ pre-BD, L/s			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
FVC pre-BD, L			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
FEV_1/FVC pre-BD, %			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Post-BD FEV_1 reversibility, n (%)‡			
Yes (current)	[redacted]	[redacted]	[redacted]
No (historical)	[redacted]	[redacted]	[redacted]
Reversibility in FEV_1, L‡			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Reversibility in FEV_1, %‡			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Reversibility in FEV_1, n (%)‡			
n	[redacted]	[redacted]	[redacted]
<12%	[redacted]	[redacted]	[redacted]
≥12 and <15%	[redacted]	[redacted]	[redacted]
≥15%	[redacted]	[redacted]	[redacted]
Time since asthma diagnosis, years§			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of exacerbations per subject in the last 12 months, n (%)			
1	[redacted]	[redacted]	[redacted]

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of exacerbations per subject in the last 12 months resulting in temporary increase in maintenance OCS dose for ≥3 consecutive days, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of exacerbations per subject in the last 12 months resulting in emergency room visit with SCS treatment, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of exacerbations per subject in the last 12 months resulting in hospitalisation with/without SCS treatment, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

NCT03406078 (SOURCE) Baseline† characteristics	Tezepelumab (n=74)	Placebo (n=76)	Total (N=150)
Min, Max	[redacted]	[redacted]	[redacted]
ICS dose group, n (%)			
Low	[redacted]	[redacted]	[redacted]
Medium	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]
OCS, n (%)			
Yes	74 (100)	76 (100)	150 (100)
No	0 (0.0)	0 (0.0)	0 (0.0)
Daily OCS dose, n (%)			
≤10 mg	[redacted]	[redacted]	[redacted]
>10 mg	[redacted]	[redacted]	[redacted]
7.5 mg	[redacted]	[redacted]	[redacted]
9 mg	[redacted]	[redacted]	[redacted]
10 mg	[redacted]	[redacted]	[redacted]
12.5 mg	[redacted]	[redacted]	[redacted]
15 mg	[redacted]	[redacted]	[redacted]
20 mg	[redacted]	[redacted]	[redacted]
25 mg	[redacted]	[redacted]	[redacted]
30 mg	[redacted]	[redacted]	[redacted]

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; EOS, eosinophil; FAS, full analysis set; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IU, International Unit; max, maximum; min, minimum; OCS, oral corticosteroid; PN, predicted normal; ppb, parts per billion; SCS, systemic corticosteroid; SD, standard deviation.
† Baseline was defined as the last non-missing measurement recorded on or prior to randomisation.
‡ Reversibility in FEV_1 (L) was calculated as post-BD FEV_1 (L) – pre-BD FEV_1 (L). Reversibility in FEV_1 (%) was calculated as (post-BD FEV_1 (L) – pre-BD FEV_1 (L)) / pre-BD FEV_1 (L) × 100%. Current post-BD reversibility was defined as FEV_1 ≥12% and ≥200 mL during screening (15–30 mins after administration of four puffs of albuterol/salbutamol). If both Visit 1 and Visit 2 values were available, the highest of the reversibility values, i.e., the largest difference (post-BD FEV_1 – pre-BD FEV_1) across the two visits was used to determine 'Yes' and 'No.' Inclusion into the study was based on current post-BD FEV_1 reversibility or on documented historical reversibility.
§ Time since asthma diagnosis was calculated as (date of randomisation – date of diagnosis/date asthma symptoms started + 1) / 365.2.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Hypotheses and methods for statistical analysis

Overviews of the approaches to statistical analysis in the pivotal Phase 2 RCT, PATHWAY, and that of its follow-on, pivotal Phase 3 RCT, NAVIGATOR, are provided in Table 18 and Table 19, respectively.

A summary of the approach to statistical analysis in the Phase 3 SOURCE trial is provided in Table 20.

Schematics of the multiple testing procedures used in the NAVIGATOR and SOURCE trials are provided in Figure 9 and Figure 10.

B.2.4.1.1 PATHWAY

Table 18: Summary of statistical analysis approach in PATHWAY

	PATHWAY
Hypothesis objective	The primary analysis was based on the ITT population. The three primary comparisons were as follows: • Tezepelumab 280 mg Q2W versus placebo • Tezepelumab 210 mg Q4W versus placebo • Tezepelumab 70 mg Q4W versus placebo
Statistical analysis	The primary endpoint was tested using a stepdown method for the three hypotheses (from the high dose [280 mg] to the medium dose [210 mg] to the low dose [70 mg] when compared with placebo) to maintain the overall Type I error rate at 0.1 (2-sided). No multiplicity adjustments were applied for secondary endpoints and supportive subgroup analyses of the primary and secondary endpoints.
Sample size, power calculation	Sample size calculations were performed for the primary endpoint of AAER, based on the negative binomial distribution. Approximately 552 subjects were to be randomised in the study, with approximately 85% of the total number of subjects designated as non-Japanese subjects (i.e. subjects enrolled at sites outside of Japan) and approximately 15% of the total number of subjects designated as Japanese subjects (i.e. subjects enrolled at sites in Japan). A total of 124 subjects per treatment group were required to detect a 40% reduction in AAER for each tezepelumab dose group compared with placebo group, assuming an AER of 0.7 in the placebo group, a 2-sided significance level of 0.1, 80% power, and a dispersion parameter of 0.7 based on the negative binomial distribution. The 2-sided significance level of 0.1 was applied to a hypothesis of comparing a single tezepelumab dose group to placebo group. The AER of 0.7 in the placebo group was estimated based on internal and external studies with a similar subject population (before considering dropouts). The dispersion parameter of 0.7 was selected from the mepolizumab study in subjects with severe, eosinophilic asthma (111). The sample size was increased to 138 per treatment group to accommodate a 10% loss of information due to dropouts. The minimal detectable difference was approximately a 28% reduction in AAER. The minimum acceptable reduction in the AAER of 40% for the study population was based upon an expected reduction of approximately 50% in a Th2-driven asthma population, which appeared to be achievable in competitors which targeted Th2 cytokines (e.g. IL-13, IL-5) and a more modest reduction in a non-Th2 asthma population for which there were little data and no current competitors.
Stratification of subjects	Prior to randomisation, subjects were stratified by study site (non-Japanese and Japanese), and then blood EOS count (≥ or <250 cells/μL) and by ICS dose level (medium or high). Subjects taking mOCS were automatically assigned to the high-dose ICS strata. There was a total of eight strata: four strata for non-Japanese subjects and four identical strata for Japanese subjects. Subjects were stratified as follows: • High blood EOS count (≥250 cells/μL) and medium ICS dose level • High blood EOS count (≥250 cells/μL) and high ICS dose level

	PATHWAY
	• Low blood EOS count (<250 cells/μL) and medium ICS dose level • Low blood EOS count (<250 cells/μL) and high ICS dose level To be classified as being on high-dose ICS, subjects had to be on a total daily dose of >500 μg fluticasone dry powder inhaler, or a total daily dose of >440 μg fluticasone metered dose inhaler or equivalent. To be classified as being on medium-dose ICS, subjects had to be on a total daily dose (sum of all ICS) of 250–500 μg fluticasone dry powder inhaler or a total daily dose of 220–440 μg fluticasone metered dose inhaler or equivalent. At least 50% of the total subjects were to be enrolled in the high blood EOS stratum (≥250 cells/μL), and ≥40% of the subjects in each blood EOS stratum were to be receiving high-dose ICS. Once the required number of subjects had been enrolled into a stratum, any subjects already in screening/run-in could be enrolled into that stratum if eligible. Thereafter, the stratum was closed, and no further subjects could be enrolled into it.
Data management, patient withdrawals	• In the analysis of the primary endpoint (AAER at Week 52) the logarithm of the follow-up time was employed as an offset variable in the negative binomial regression model to adjust for subjects having different follow-up times • For the continuous secondary endpoints, the MMRM approach was used to analyse the longitudinal data to handle missing data • For the time to event secondary endpoints, the early dropouts who did not experience the event were censored at the time of discontinuation • Sensitivity analysis on the secondary endpoints of change from baseline in pre-BD FEV_1 and asthma overall symptom score using LOCF approach to impute missing data was performed • Sensitivity responder analysis on ACQ-6 and AQLQ(S)+12 based on LOCF imputation was also performed

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; CFB, change from baseline; EOS, eosinophil; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; mOCS, maintenance oral corticosteroid treatment; PBO, placebo; teze, tezepelumab.

B.2.4.1.2 NAVIGATOR

Table 19: Summary of statistical analysis approach in NAVIGATOR

	NAVIGATOR
Hypothesis objective	The following 2-sided hypotheses were evaluated: Primary endpoint (all subjects): • **H01:** AAER ratio over 52 weeks (teze/PBO) = 1, vs • **H11:** AAER ratio over 52 weeks (teze/PBO) ≠ 1 A rate ratio <1 indicates superiority of teze. Primary endpoint (subjects with baseline EOS <300 mL): • **H02:** AAER ratio over 52 weeks (teze/PBO) = 1, vs • **H12:** AAER ratio over 52 weeks (teze/PBO) ≠ 1 A rate ratio <1 indicates superiority of teze. Key secondary endpoints (all subjects): • **H03:** Diff in mean CFB in pre-BD FEV_1 at 52 weeks (teze–PBO) = 0, vs • **H13:** Diff in mean CFB in pre-BD FEV_1 at 52 weeks (teze–PBO) ≠ 0 A diff in means >0 indicates superiority of teze.

	NAVIGATOR
	• **H04a:** Diff in mean CFB in AQLQ(S)+12 total score at 52 weeks (teze–PBO) = 0 • **H14a:** Diff in mean CFB in AQLQ(S)+12 total score at 52 weeks (teze–PBO) ≠ 0 A diff in means >0 indicates superiority of teze. • **H04b:** Diff in mean CFB in ACQ-6 score at 52 weeks (teze–PBO) = 0 • **H14b:** Diff in mean CFB in ACQ-6 score at 52 weeks (teze–PBO) ≠ 0 A diff in means <0 indicates superiority of teze. • **H05:** Diff in mean CFB in weekly mean ASD score at 52 weeks (teze–PBO) = 0 • **H15:** Diff in mean CFB in ASD score at 52 weeks (teze–PBO) ≠ 0 A diff in means <0 indicates superiority of teze.
Statistical analysis	A hierarchical testing strategy (illustrated in Figure 9) was implemented to test for superiority of tezepelumab over placebo in each of the primary and key secondary endpoints, whilst controlling the overall Type 1 error rate at 0.05 (2-sided). The overall Type 1 error rate was strongly controlled at the 0.05 level across the primary and key secondary endpoints. The primary endpoint (in all subjects) was tested at the 0.01 level to further ensure statistically persuasive evidence. If the primary analysis of AAER in all subjects observed p≤0.01, the trial would be declared successful. In order to assess the primary objective of effect across the all-comer population, the subgroup of subjects with baseline EOS <300/μL[†] was added into the multiple testing procedure. A hierarchical testing strategy was applied, ordered by endpoint clinical relevance. Level 1: The null hypothesis H01 was tested at a 2-sided 1% significance level regarding the primary endpoint (AAER) in all subjects. Level 2: If H01 was rejected at the 2-sided 1% significance level, then the null hypothesis H02 was to be tested at a 2-sided 5% significance level regarding the AAER in subjects with baseline EOS <300/μL. Level 3: If H02 was rejected at the 2-sided 5% significance level, then the null hypothesis H03 was to be tested at a 2-sided 5% significance level regarding CFB in pre-BD FEV_1. Level 4: If H03 was rejected at the 2-sided 5% significance level, then the null hypotheses H04a and H04b were to be simultaneously tested at an overall 2-sided 5% significance level regarding: • CFB in AQLQ(S)+12 total score • CFB in ACQ-6 score Using a truncated Hochberg approach. In general, under this approach, the higher of the two ordered p-values within Level 4 would be evaluated at a $\gamma\alpha+(1-\gamma)\alpha/2$ significance level (2-sided), and the lower of the two ordered p-values within Level 4 would be evaluated at a $\gamma\alpha/2+(1-\gamma)\alpha/2$ significance level (2-sided), where $\alpha=0.05$, and where γ is the truncation parameter ($0\leq\gamma\leq1$). An intermediate choice $0<\gamma<1$ of the truncation parameter represents a choice between these extremes of regular Hochberg (corresponding to $\gamma=1$) and Bonferroni approaches ($\gamma=0$), balancing considerations of how stringent hypothesis testing should be in Level 4 in order to claim significance, versus the ability to subsequently claim significance from formal hypothesis testing in Level 5. In NAVIGATOR, γ was set to 0.5. Using this choice of truncation parameter, the higher of the two Level 4 p-values was to be evaluated at a 3.75% significance level (2-sided). If it was significant at the 3.75% level, then both hypotheses H04a and H04b would be rejected, and testing would proceed to Level 5. If it was not significant at the 3.75% level, then the lower of the two Level 4 p-values was evaluated at a 2.5% significance level (2-sided). If it was significant, then the relevant null hypothesis (either H04a or H04b) was to be rejected, and testing to proceed to Level 5. If it was (also) not significant, then formal testing was to stop at Level 4.

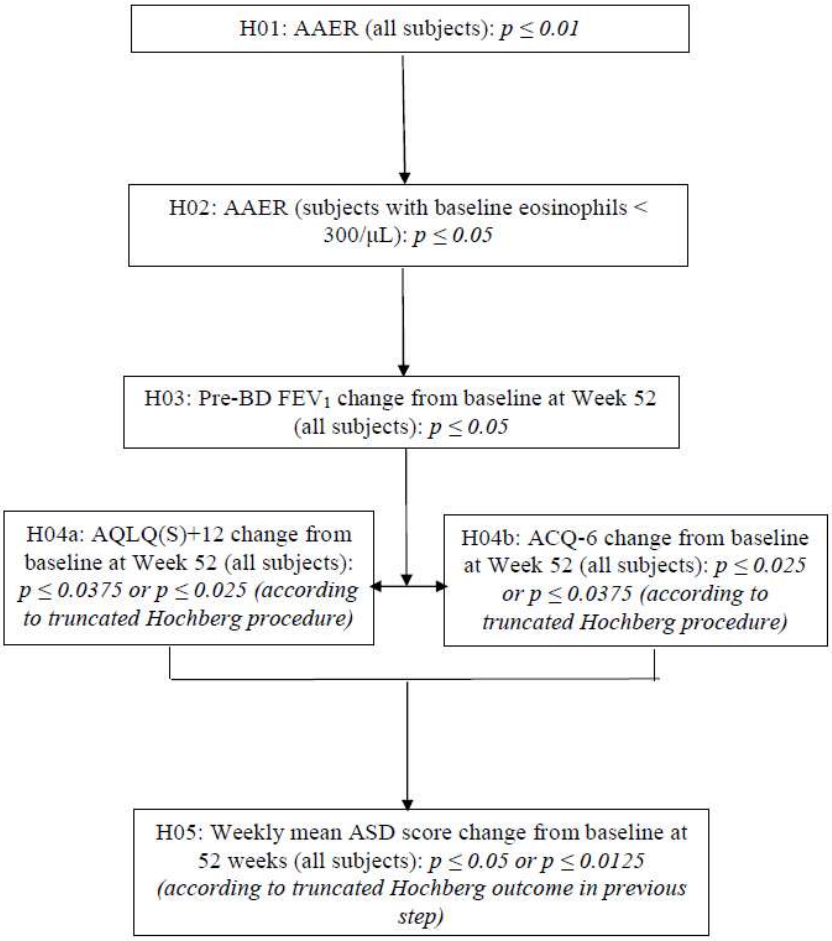
	NAVIGATOR
	Level 5: The null hypothesis H05 was tested at the significance level retained from Level 4, which depended on the outcomes in Level 4 as follows: • Case 1: If both comparisons in Level 4 exhibited statistical significance, then H05 would be tested at a 2-sided 5% significance level with regard to CFB in weekly mean ASD score. • Case 2: If only the comparisons in Level 4 exhibited statistical significance, then H05 was to be tested at the 2-sided significance level $\alpha-[\gamma\alpha+(1-\gamma)\alpha/2]$ retained from Level 4, where $\alpha=0.05$. Using the proposed choice of $\gamma=0.5$, if both H04a and H04b were rejected in Level 4, then H05 in Level 5 was to be tested at a 2-sided 5% significance level (Case 1). If only one of H04a and H04b was rejected in Level 4, then H05 in Level 5 was to be tested at a 2-sided 1.25% significance level (Case 2).
Sample size, power calculation	Approximately 1,060 subjects were to be randomly assigned to study treatment using 1:1 allocation between the two treatments. Since the primary analysis of the primary endpoint would include all available data, including after treatment discontinuation, no need was envisaged to adjust the number of subjects planned to be randomised in order to obtain a number of evaluable subjects. With 530 subjects per treatment group, it was estimated that, using the multiple testing procedure described above with an overall Type 1 error control at $\alpha=0.05$ and a Type 1 error control for the primary endpoint at $\alpha=0.01$, the power for the primary and the key secondary endpoints would be at least 90%. The Type 1 error control at $\alpha=0.01$ for the primary endpoint was chosen to further ensure statistically persuasive evidence. For the primary endpoint, assuming a placebo rate of 0.9 per year, a shape parameter of 2.4 (overdispersion), and a dropout rate of 10% (assumed uniform over the study), there would be at least 99% power to detect a rate reduction of 50% at a 2-sided significance level of 1%. For AAER in subjects with baseline EOS <300/µL, assuming a placebo rate of 0.6 and assuming that half of subjects would be in this subgroup (i.e. 265 subjects per treatment group), there would be 94% power to detect a rate reduction of 50% at a 2-sided significance level of 5%, with the same shape parameter and dropout assumptions as above. The minimum rate reduction that would yield statistical significance with the above assumptions was 27%. For each of the following four key secondary endpoints, CFB in pre-BD FEV_1, AQLQ(S)+12 total score, ACQ-6, and weekly mean ASD score, the nominal power was 95% or higher (using a nominal 2-sided significance level of 5%), assuming standard deviations of 400 mL and 1.3, 1.3, and 1.3 units respectively, and true differences of 100 mL and 0.3, 0.3, and 0.3 units respectively. The minimum detectable differences, under the above assumptions, were 50 mL for FEV_1, 0.16 for AQLQ(S)+12 total score, and –0.16 for each of ACQ-6 and ASD scores.
Distribution of subjects across three key clinical factors	Enrolment of the study population was monitored to ensure a broad subject distribution across three different key clinical factors: • Approximately 20% of the total study population were to be subjects who were treated with a total daily dose of medium dose ICS as well as on at least one additional maintenance asthma controller medication with or without mOCS in the 3 months prior to date of informed consent. • Approximately 40% of subjects in the study were required to have had at least three exacerbations in the prior 12 months, with the remaining subjects having had exactly two exacerbations. • The study also aimed to randomise a similar percentage of subjects with EOS <300 cells/µL and ≥300 cells/µL. In addition, a reasonable number of subjects was expected to be randomised with EOS <150 cells/µL and >450 cells/µL. When the target percentage of subjects for the ICS, exacerbations, or EOS subgroups were reached, consideration was given to closing the IWRS randomisation for that subgroup (either overall or within a specific region). Once a subgroup was closed,

	NAVIGATOR
	subjects in the screening/run-in period in the closed subgroup were not randomised and were considered screen failures.
Data management, patient withdrawals	Analysis of the primary efficacy endpoint The primary analysis of the primary efficacy endpoint (AAER over 52 weeks) quantified the effect of the initially randomised treatment, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications post investigational product discontinuation. The analysis of the primary efficacy endpoint therefore included all available data after treatment discontinuation. Subjects were encouraged to continue to undergo applicable study-related visits/procedures for the full 52-week period even after premature discontinuation of the investigational product. Consequently, subjects lost to follow-up and subjects who withdrew their consent were the only source of missing information for the primary analysis. Missing data from study discontinuation were modelled based on what was observed during the study using direct likelihood approaches – a valid approach under the assumption that data were missing at random. AAER in the tezepelumab group was compared with that seen in the placebo group using a negative binomial model. This model was used to perform the statistical test described above, and to estimate the treatment effect and both its 99% and 95% confidence intervals. The response variable in the model was the number of asthma exacerbations experienced by a subject over the 52-week study period (or shorter duration if not followed up for the full 52 weeks). Treatment, region, age (adolescents or adults) and history of exacerbations (2 or >2 in previous 12 months) were included as factors in this model. The logarithm of the time at risk for exacerbation in the study was used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occurred. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, were not included in the calculation of time at risk for exacerbation. For the purpose of showing consistency of treatment effect across continuous baseline biomarkers (including, but not necessarily limited to, baseline EOS, FeNO, and total IgE), the AAER was modelled across the continuous biomarker using methods such as moving average or smoothing splines. For the purpose of showing consistency of treatment effect across categorical baseline or demographic variables (including, but not necessarily limited to, high and low EOS categories, high and low FeNO categories, specific IgE status, age categories, gender, race, history of exacerbations, asthma controller therapy at randomisation, and medium/high ICS dose), a similar model was fitted as for the primary analysis with additional factors for the relevant subgroup variable and its interaction with treatment. This included the analysis of AAER in subjects with baseline EOS <300/μL. Analysis of key secondary efficacy endpoints The main analysis of the key secondary endpoints (changes from baseline to Week 52 for each of pre-BD FEV_1, AQLQ(S)+12 total score, ACQ-6 score, and weekly mean ASD score) quantified the effect of the initially randomised treatment at Week 52, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications, including for subjects who discontinued study treatment prior to Week 52. This analysis therefore included all available data after treatment discontinuation. Missing data from study discontinuation were modelled based on what was observed during the study using direct likelihood approaches – a valid approach under the assumption that data were missing at random. Change from baseline for the key secondary endpoints in the tezepelumab group were compared with that seen in the placebo group using an MMRM model. This model was used to perform the statistical tests described above and to estimate the treatment effect at Week 52 and its 95% confidence interval for each endpoint. The response variable in the model was the CFB at each scheduled post-randomisation visit up to and including Week 52, and irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region, age (adolescents or adults), and treatment by visit

	NAVIGATOR
	interaction were included as factors in this model. Baseline of the corresponding endpoint was also included in the model as a continuous linear covariate. Unstructured covariance was assumed to model the relationship between pairs of response variables taken at different visits on the same subject. If the MMRM model failed to converge with unstructured covariance, a pre-specified approach for selecting a simpler covariance structure was used. The Kenward-Roger approximation to estimating the degrees of freedom was used for tests of fixed effects derived from the MMRM model. The consistency of treatment effects across continuous and categorical demographic/baseline variables was investigated in a similar manner to the primary endpoint. In the case of categorical variables, appropriate terms were added to the MMRM model, including a treatment by visit by subgroup interaction term, to enable the treatment effects within each subgroup category at Week 52 to be estimated.

Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; CFB, change from baseline; diff, difference; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IWRS, Interactive Web Response System; MMRM, mixed-effects model for repeated measures; mOCS, maintenance oral corticosteroid treatment; PBO, placebo; teze, tezepelumab.
† This was to support US FDA breakthrough designation in patients without an eosinophilic phenotype.

Figure 9: Multiple testing procedure used in NAVIGATOR



Abbreviations: AAER, annualised asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; BD, bronchodilator; FEV_1, forced expiratory volume in the first second.

B.2.4.1.3 SOURCE

Table 20: Summary of statistical analysis approach in SOURCE

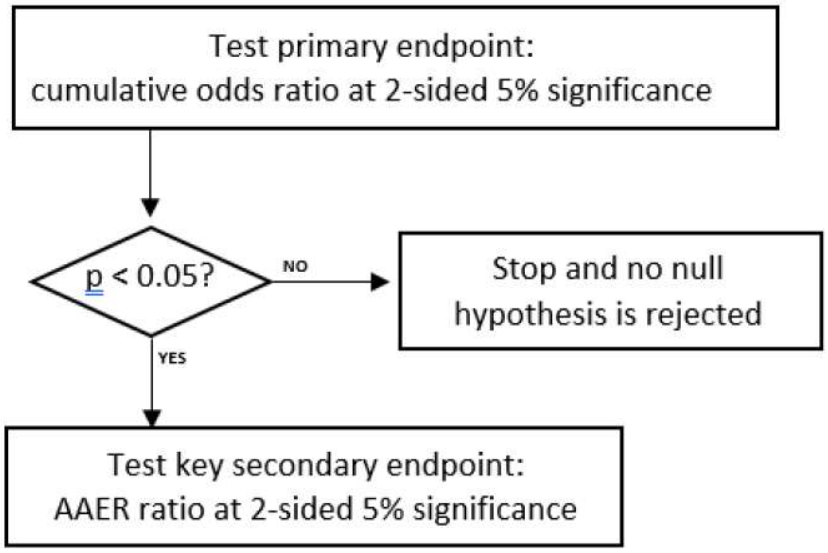
	SOURCE
Hypothesis objective	The following 2-sided hypotheses were evaluated: Primary endpoint (all subjects): • **H01:** Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (teze/PBO) = 1, vs • **H11:** Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (teze/PBO) ≠ 1 For five ordered categories, there were four possible cumulative odds for each treatment group, corresponding to the four different possible binary splits, which were defined as follows: • Category 1 vs categories 2, 3, 4, 5 • Categories 1, 2 vs categories 3, 4, 5 • Categories 1, 2, 3 vs categories 4, 5 • Categories 1, 2, 3, 4 vs category 5 Where the ordered categories for OCS daily dose reduction were in turn defined as: • Category 1: 90–100% reduction • Category 2: 75–<90% reduction • Category 3: 50–<75% reduction • Category 4: >0–<50% reduction • Category 5: no reduction or an increase This hypothesis assumed that the four possible odds ratios between the two treatments as defined above were the same (proportional odds assumption). The direction of superiority of teze is indicated by an odds ratio >1. Key secondary endpoints (all subjects): • **H02:** AAER ratio over 52 weeks (teze/PBO) = 1, vs • **H12:** AAER ratio over 52 weeks (teze/PBO) ≠ 1
Statistical analysis	A hierarchical testing strategy (illustrated in Figure 10) was implemented to test for superiority of tezepelumab over placebo in the primary and key secondary endpoints, whilst controlling the overall Type 1 error rate at 0.05 (2-sided). The 2-sided hypotheses outlined above were evaluated at the 0.05 significance level. All other hypothesis testing in the study was considered exploratory. To account for multiplicity when testing the primary and secondary endpoints, a hierarchical testing procedure was applied, with the hypotheses tested as outlined above: Level 1: The null hypothesis H01 was tested at a 2-sided significance with regard to the primary endpoint (percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control). Level 2: If H01 was rejected, the null hypothesis H02 was tested at a 2-sided significance level with regard to the key secondary endpoint (AAER ratio over 48 weeks).
Sample size, power calculation	Approximately 152 subjects were to be randomly assigned to study treatment using 1:1 allocation between the two treatments. Since the primary analysis of the primary endpoint was to include all randomised subjects as far as possible, no need was envisaged to adjust the number of subjects planned to be randomised in order to obtain a number of evaluable subjects. With 76 subjects per treatment group, it was estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint of OCS reduction would be at least 90%, assuming:

	SOURCE
	• An odds ratio of 2.75 and the proportional odds assumption The proportion of subjects in the five different dose reduction categories was similar to results reported in the Steroid Reduction with Mepolizumab Study (112). The following proportions were assumed for placebo: • Category 1 (90–100% reduction): 10% of subjects • Category 2 (75–<90% reduction): 10% of subjects • Category 3 (50–<75% reduction): 15% of subjects • Category 4 (>0–<50% reduction): 15% of subjects • Category 5 (no reduction or an increase): 50% of subjects The minimal detectable odds ratio still being significant with the above assumptions was 1.86. For the key secondary endpoint of reduction in the AAER, 76 subjects per group had >80% power to reject the null hypothesis for rate ratio up to 0.39, using a 2-sided significance level and assuming: • A placebo rate of 1.3 exacerbations/year in this study population • A conservative assumption on the dispersion parameter (2.4) Uniform dropout of 10%
Targeted enrolment of subjects with EOS ≥300 cells/µl	Approximately 35% of subjects were to have EOS ≥300 cells/µL at enrolment. When the target percentage of subjects for the EOS subgroup in a region was reached, consideration was given to closing the IWRS randomisation for that subgroup (either overall or within a specific region). Once a subgroup was closed, subjects in the screening/run-in period in the closed subgroup were not allowed to be randomised and were considered screen failures.
Data management, patient withdrawals	Analysis of the primary efficacy endpoint The primary analysis of the primary efficacy endpoint quantified the effect of the initially randomised treatment, regardless of the treatments that subjects actually received. Subjects were encouraged to continue to undergo applicable study-related visits/procedures for the full 48-week period even after premature discontinuation of investigational product. This analysis therefore included all available data after treatment discontinuation for subjects who continued to attend monthly visits either at site or by telephone. The primary endpoint in the tezepelumab group was compared with that in the placebo group using a proportional odds (ordinal logistic regression) model. This model was used to perform the statistical test described above, and to estimate the treatment effect and its 95% confidence interval. The response variable in the model was the ordered category number (1–5) at Week 48 as defined above. Treatment and region were included as factors in this model. Baseline OCS dose was also included in the model as a continuous (linear) covariate. The validity of the proportional odds assumption across the categories of the response variable for the three factors fitted in the model were assessed by plotting empirical logits for each predictor separately. A score test statistic was also calculated, but as it is known to be liberal, it was interpreted with caution, and was used together with the empirical logit plots to decide if the proportional odds assumption was valid. If the proportional odds assumption was not satisfied due to non-proportional effects of region or baseline OCS dose across the response, then a partial proportional odds model was fitted, using the UNEQUALSLOPES option within SAS, to allow different effects across the categorical response for factors shown to be non-proportional. If the proportional odds assumption was not satisfied due to non-proportional effects of treatment across the response, then results were presented from the proportional odds model, but results of the analysis were confirmed using a Wilcoxon rank sum test stratified by region. Analysis of key secondary efficacy endpoint The main analysis of the key secondary endpoint (AAER over 48 weeks) quantified the effect of the initially randomised treatment, regardless of the treatments that subjects

	SOURCE
	actually received. This analysis therefore included all available data after treatment discontinuation until the end of the planned treatment period. Subjects were encouraged to continue to undergo applicable study-related visits/procedures for the full 48-week period even after premature discontinuation of investigational product. Consequently, subjects lost to follow-up, subjects who died, and subjects who withdraw their consent were the only source of missing information for the primary analysis. Missing data from early study withdrawal were modelled based on what was observed during the study using direct likelihood approaches – a valid approach under the assumption that data were missing at random. AAER in the tezepelumab group was compared with that seen in the placebo group using a negative binomial model. This model was used to estimate the rate ratio and its 95% confidence interval. The response variable in the model was the number of asthma exacerbations experienced by a subject over the 48-week planned treatment period (or shorter duration if not followed up for the full 48 weeks). Treatment, region and history of exacerbations (≤2 or >2 in previous 12 months) were included as factors in this model. The logarithm of the time at risk (in years) for exacerbation in the study was used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occurred. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, were not included in the calculation of time at risk for exacerbation.

Abbreviations: AAER, annualised asthma exacerbation rate; EOS, eosinophil; IWRS, Interactive Web Response System; OCS, oral corticosteroid; PBO, placebo; teze, tezepelumab.

Figure 10: Testing procedure used in SOURCE



Abbreviations: AAER, annualised asthma exacerbation rate.

B.2.4.2 Definitions of analysis sets

Analysis sets used in the PATHWAY, NAVIGATOR, and SOURCE trials are defined in

Table 21, Table 22, and

Table 23, respectively

Table 21: Definitions of analysis sets (PATHWAY)

Analysis set	
ITT population	Subjects who were randomised and received any investigational product were included in the ITT population, and subjects were analysed according to their randomised treatment group. This was the primary efficacy population
As-treated population	Subjects who received any investigational product were included in the as-treated population and subjects were analysed according to the treatment they actually received
Per-protocol population	Subjects who did not have significant protocol violations and received at least 80% of the intended doses of investigational product were included in the per-protocol population, and subjects were analysed according to the treatment they actually received

Abbreviations: ITT, intent-to-treat.

Table 22: Definitions of analysis sets (NAVIGATOR)

Analysis set	
All subjects analysis set	All enrolled subjects who signed the informed consent form, including screening failures.
Randomised subjects analysis set	All subjects randomised to study treatment, irrespective of whether investigational product was subsequently taken.
Full analysis set	All subjects randomised to study treatment who received at least one dose of investigational product, irrespective of their protocol adherence, and continued participation in the study.
Safety analysis set	All subjects who received at least one dose of investigational product.

Table 23: Definitions of analysis sets (SOURCE)

Analysis set	
All subjects analysis set	All enrolled subjects who signed the informed consent form, including screening failures.
Randomised subjects analysis set	All subjects randomised to study treatment, irrespective of whether investigational product was subsequently taken.
Full analysis set	All subjects randomised to study treatment who received at least one dose of investigational product, irrespective of their protocol adherence, and continued participation in the study.
Safety analysis set	All subjects who received at least one dose of investigational product.

B.2.4.3 Participant flow in the relevant randomised controlled trials

B.2.4.3.1 PATHWAY

A total of 918 subjects were enrolled in PATHWAY, of which 550[a] were randomised to treatment with either:

[a] A total of 584 subjects were actually randomised; however 34 subjects from one site in the US were excluded from the study due to anomalous data and noncompliance with good clinical practice

- Tezepelumab 70 mg once every 4 weeks (Q4W) (n=138), or
- Tezepelumab 210 mg Q4W (n=137), or
- Tezepelumab 280 mg once every two weeks (Q2W) (n=137), or
- Placebo (n=138)

Subject numbers in each analysis set of PATHWAY are presented in Table 24.

Of the 550 subjects randomised to treatment, 496 subjects (90.2%) completed treatment, and the remaining 54 subjects (9.8%) did not complete treatment. A total of 494 subjects (89.8%) completed the study (Table 25).

Table 24: Numbers of subjects in each analysis set in PATHWAY

Population	Tezepelumab				Placebo	Total
	70 mg Q4W	210 mg Q4W	280 mg Q2W	Total		
Subjects randomised	138	137	137	412	138	550
ITT population†	138	137	137	412	138	550
As-treated population‡	138	137	137	412	138	550
Per-protocol population§	114	106	108	328	121	449

Abbreviations: ITT, intent-to-treat; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
† Subjects who were randomised and received any investigational product were included in the ITT population, and subjects were analysed according to their randomised treatment group. This was the primary efficacy population.
‡ Subjects who received any investigational product were included in the as-treated population and subjects were analysed according to the treatment they actually received.
§ Subjects who did not have significant protocol violations and received at least 80% of the intended doses of investigational product were included in the per-protocol population, and subjects were analysed according to the treatment they actually received.

Table 25: Completions/withdrawals in PATHWAY

	Tezepelumab				Placebo	Total
	70 mg Q4W	210 mg Q4W	280 mg Q2W	Total		
Randomised and received treatment, n (%)	138	137	137	412	138	550
Completed treatment, n (%)	129 (93.5)	121 (88.3)	117 (85.4)	367 (89.1)	129 (93.5)	496 (90.2)
Did not complete treatment, n (%)	9 (6.5)	16 (11.7)	20 (14.6)	45 (10.9)	9 (6.5)	54 (9.8)
Reasons for not completing treatment, n (%)						
Lost to follow-up	0	1 (0.7)	2 (1.5)	3 (0.7)	0	3 (0.5)
Other†	6 (4.3)	6 (4.4)	7 (5.1)	19 (4.6)	3 (2.2)	22 (4.0)
Withdrawal of consent	3 (2.2)	7 (5.1)	8 (5.8)	18 (4.4)	5 (3.6)	23 (4.2)
Adverse event	0	2 (1.5)	3 (2.2)	5 (1.2)	1 (0.7)	6 (1.1)
Completed study, n (%)‡	127 (92.0)	122 (89.1)	115 (83.9)	364 (88.3)	130 (94.2)	494 (89.8)
Reasons for not completing study, n (%)						
Withdrawal of consent	4 (2.9)	7 (5.1)	10 (7.3)	21 (5.1)	4 (2.9)	25 (4.5)
Death	1 (0.7)	0	0	1 (0.2)	0	1 (0.2)
Lost to follow-up	0	1 (0.7)	2 (1.5)	3 (0.7)	0	3 (0.5)
Other§	6 (4.3)	7 (5.1)	10 (7.3)	23 (5.6)	4 (2.9)	27 (4.9)
Non-Japanese, n (%)	135 (97.8)	132 (96.4)	132 (96.4)	399 (96.8)	132 (95.7)	531 (96.5)
Japanese, n (%)	3 (2.2)	5 (3.6)	5 (3.6)	13 (3.2)	6 (4.3)	19 (3.5)

Abbreviations: AE, adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event.
† Other reasons included subject's decision, adverse event, failure to meet eligibility criteria, visit out of window, sponsor decision, lack of available investigational product, pregnancy, use of prohibited medication, and missed dose.
‡ Completion of study was defined as the treated subject was followed through to the last protocol-specified visit/assessment.
§ Other reasons included missed dose, subject's decision, adverse event, serious adverse event, failure to meet eligibility criteria, lack of available investigational product, sponsor decision, pregnancy, and use of prohibited medication.

B.2.4.3.2 NAVIGATOR

A total of 2,420 subjects were enrolled in NAVIGATOR, of which 1,061 were randomised to treatment during the double-blind phase with either:

- Tezepelumab 210 mg Q4W (n=529), or
- Placebo (n=532)

Subject numbers in each analysis set of NAVIGATOR are presented in Table 26.

Table 26: Numbers of subjects in each analysis set in NAVIGATOR

Population	Tezepelumab 210 mg Q4W	Placebo	Total
Subjects randomised	529	532	1,061
Full analysis set†	528	531	1,059
Safety analysis set‡	528	531	1,059

Abbreviations: Q4W, once every 4 weeks.
† All subjects randomised to study treatment who received at least one dose of investigational product, irrespective of their protocol adherence and continued participation in the study.
‡ All subjects who received at least one dose of investigational product.

A CONSORT flow chart for NAVIGATOR is presented in Figure 11. Of the 1,061 subjects randomly assigned to treatment, 1,059 proceeded to receive treatment. A total of 966 (91.0%) subjects completed treatment and 93 (8.7%) subjects withdrew (Table 27). Two randomised patients (one in each treatment group) did not receive any treatment. A total of 60 (5.7%) subjects discontinued treatment but completed study assessments. The most common reason for treatment discontinuation was withdrawal by the subject. A total of 954 (89.9%) subjects completed the whole trial (i.e. completed treatment and study).

In the tezepelumab group, a total of 415 (78.0%) subjects entered an extension study (DESTINATION) while 72 (14.8%) in this group completed the follow-up period but did not enter the extension study.

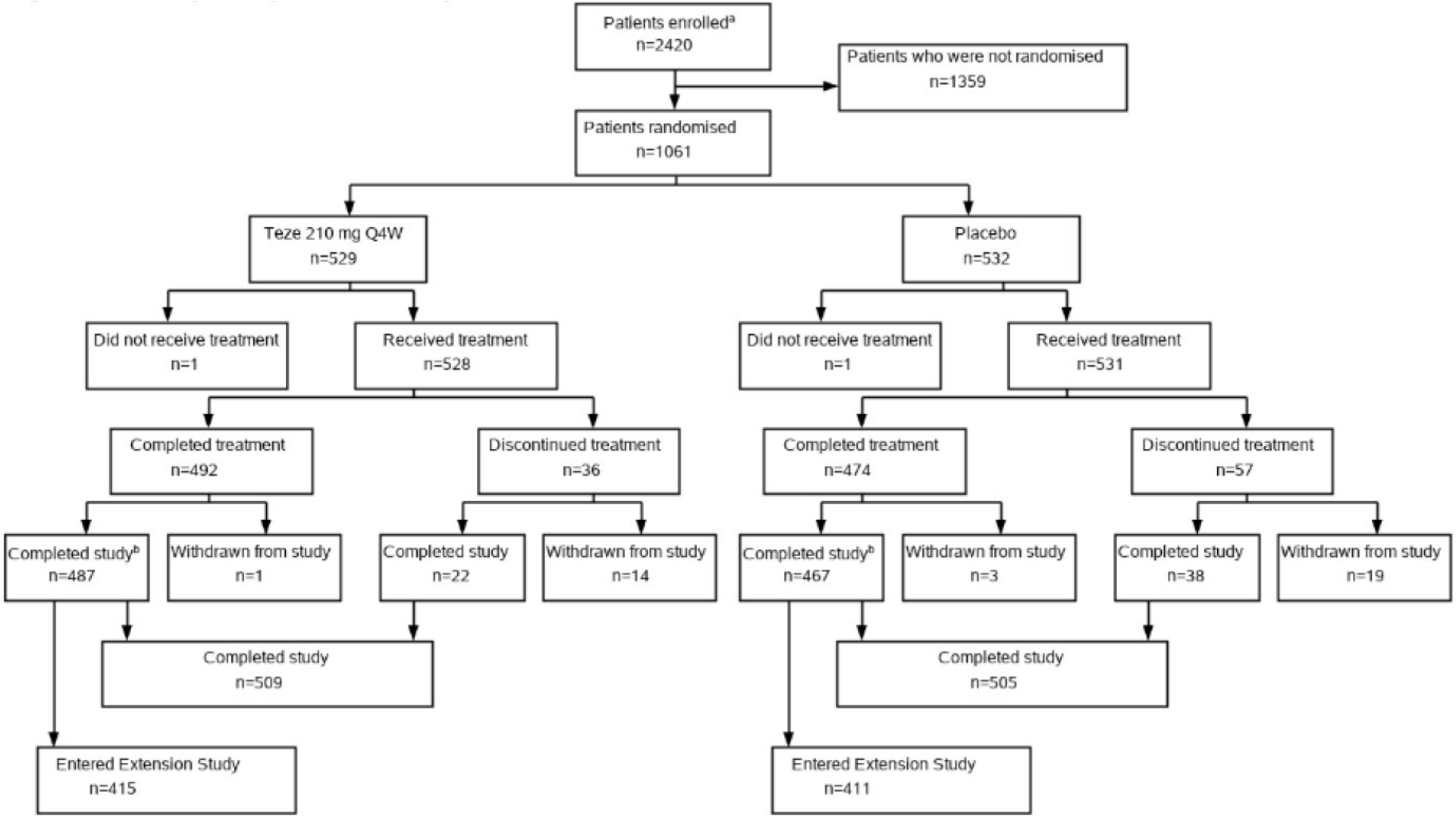
Table 27: Completions/withdrawals in NAVIGATOR

	Tezepelumab 210 mg Q4W	Placebo	Total
Randomised, n (%)	529 (100.0)	532 (100.0)	1,061 (100.0)
Received treatment, n (%)	528 (99.8)	531 (99.8)	1,059 (99.8)
Completed treatment, n (%)	492 (93.0)	474 (89.1)	966 (91.0)
Discontinued treatment, n (%)	36 (6.8)	57 (10.7)	93 (8.8)
Withdrawal by subject	14 (2.6)	26 (4.9)	40 (3.8)
Adverse event	7 (1.3)	14 (2.6)	21 (2.0)

	Tezepelumab 210 mg Q4W	Placebo	Total
Protocol deviation	2 (0.4)	1 (0.2)	3 (0.3)
Development of study-specific withdrawal criteria	4 (0.8)	5 (0.9)	9 (0.8)
Lost to follow-up	5 (0.9)	0 (0.0)	5 (0.5)
Other	4 (0.8)	11 (2.1)	15 (1.4)
Due to COVID-19 pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued treatment but completed study assessments	22 (4.2)	38 (7.1)	60 (5.7)
Completed study, n (%)†	509 (96.2)	505 (94.9)	1,014 (95.6)
Withdrew from study, n (%)	16 (3.0)	23 (4.3)	39 (3.7)
Death	0 (0.0)	2 (0.4)	2 (0.2)
Lost to follow-up	5 (0.9)	2 (0.4)	7 (0.7)
Withdrawal by subject	8 (1.5)	15 (2.8)	23 (2.2)
Other	3 (0.6)	4 (0.8)	7 (0.7)
Due to COVID-19 pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Completed treatment and completed study, n (%)	487 (92.1)	467 (87.8)	954 (89.9)

Abbreviations: Q4W, once every 4 weeks.
† Includes subjects who completed treatment and study, and subjects who discontinued treatment but completed study assessments. A subject who did not participate in the extension study after the planned treatment period, and who did not complete the follow-up visits, was considered not to have completed the study (but to have completed treatment). Subjects discontinuing investigational product due to protocol deviation were those with severe non-compliance to the protocol.

Figure 11: CONSORT diagram for NAVIGATOR



Abbreviations: teze, tezepelumab; Q4W, once every 4 weeks.
[a] Informed consent received.
[b] Subjects who completed treatment and entered either the extension study or post-study follow-up. Four subjects in each treatment group completed treatment but were ongoing in safety follow-up at the time of the primary database lock.

B.2.4.3.3 SOURCE

A total of 243 subjects were enrolled in SOURCE of which 150 were randomised to treatment with either:

- Tezepelumab 210 mg Q4W (n=74), or
- Placebo (n=76)

Subject numbers in each analysis set of SOURCE are presented in Table 28.

Table 28: Numbers of subjects in each analysis set in SOURCE

Population	Tezepelumab 210 mg Q4W	Placebo	Total
Subjects randomised	74	76	150
Full analysis set†	74	76	150
Safety analysis set‡	74	76	150

Abbreviations: Q4W, once every 4 weeks.
† All subjects randomised to study treatment who received at least one dose of investigational product, irrespective of their protocol adherence and continued participation in the study.
‡ All subjects who received at least one dose of investigational product.

A CONSORT flow chart for SOURCE is presented in Figure 12. Of the 150 subjects randomly assigned to treatment, 137 (91.3%) subjects completed treatment and 13 (8.7%) subjects withdrew (Table 29). A total of six (4.0%) subjects discontinued treatment but completed study assessments. The most common reason for treatment discontinuation was withdrawal by the subject. A total of 135 (90.0%) subjects completed the whole trial (i.e. completed treatment and study).

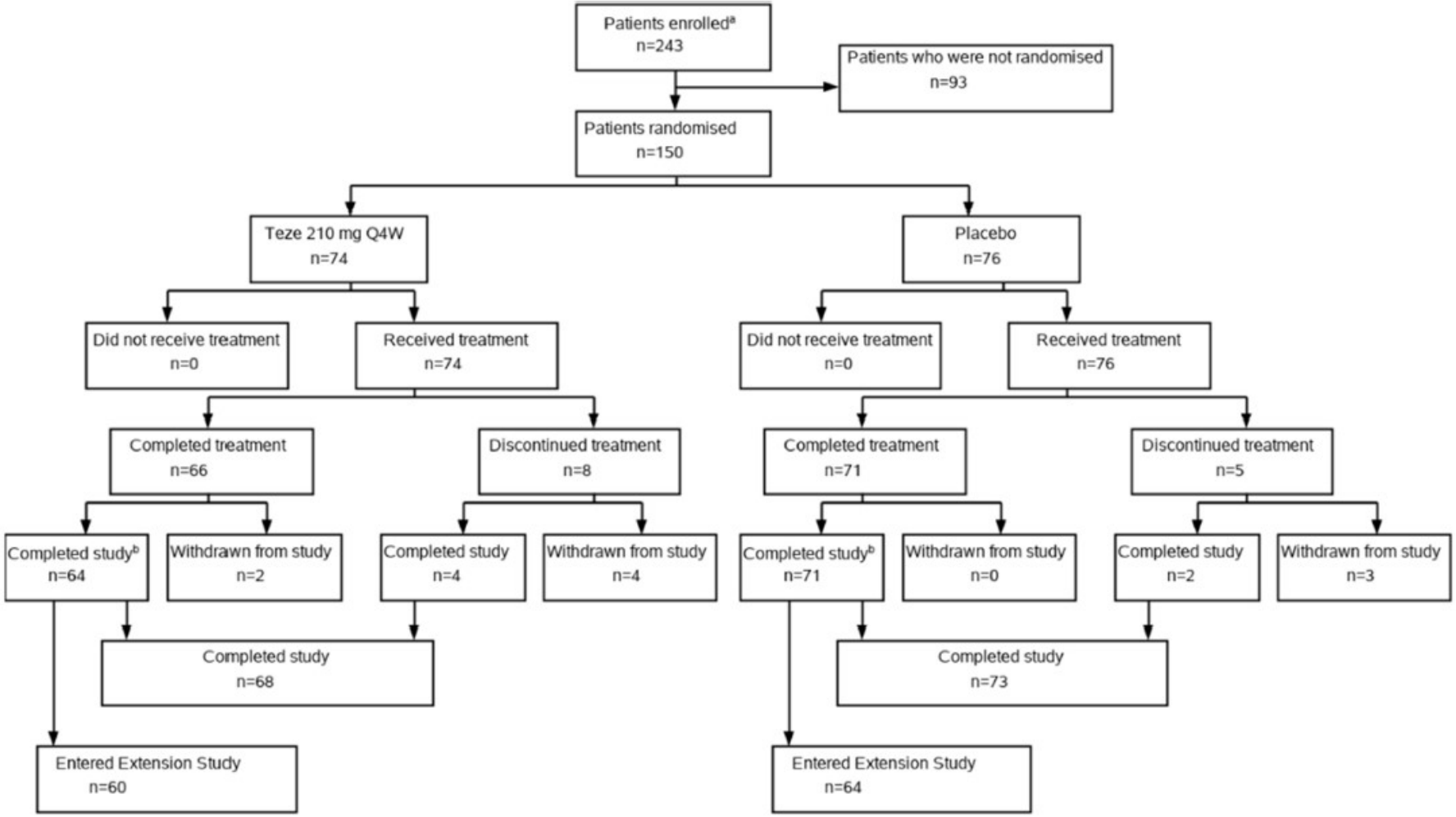
Table 29: Completions/withdrawals in SOURCE

	Tezepelumab 210 mg Q4W	Placebo	Total
Randomised, n (%)	74 (100.0)	76 (100.0)	150 (100.0)
Received treatment, n (%)	74 (100.0)	76 (100.0)	150 (100.0)
Completed treatment, n (%)	66 (89.2)	71 (93.4)	137 (91.3)
Discontinued treatment, n (%)	8 (10.8)	5 (6.6)	13 (8.7)
Withdrawal by subject	4 (5.4)	2 (2.6)	6 (4.0)
Adverse event	1 (1.4)	2 (2.6)	3 (2.0)
Development of study-specific withdrawal criteria	1† (1.4)	0 (0.0)	1 (0.7)
Lost to follow-up	0 (0.0)	1 (1.3)	1 (0.7)
Other	2 (2.7)	0 (0.0)	2 (1.3)
Due to COVID-19 pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued treatment but completed study assessments	4 (5.4)	2 (2.6)	6 (4.0)

	Tezepelumab 210 mg Q4W	Placebo	Total
Completed study, n (%)‡	68 (91.9)	73 (96.1)	141 (94.0)
Withdrew from study, n (%)	6 (8.1)	3 (3.9)	9 (6.0)
Death	1 (1.4)	0 (0.0)	1 (0.7)
Lost to follow-up	0 (0.0)	1 (1.3)	1 (0.7)
Withdrawal by subject	5 (6.8)	2 (2.6)	7 (4.7)
Due to COVID-19 pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Completed treatment and completed study, n (%)	64 (86.5)	71 (93.4)	135 (90.0)

Abbreviations: Q4W, once every 4 weeks.
† Subject withdrew from the study as they were unable to continue due to an adverse event (preferred term: invasive breast carcinoma).
‡ Includes subjects who completed treatment and study, and subjects who discontinued treatment but completed study assessments. A subject who did not participate in the extension study after the planned treatment period, and who did not complete the follow-up visits, was considered not to have completed the study (but to have completed treatment). Subjects discontinuing investigational product due to protocol deviation were those with severe non-compliance to the protocol. Subjects who were not randomised included subjects not eligible to start the optimisation phase as well as subjects for whom oral corticosteroids optimisation was not achieved.

Figure 12: CONSORT diagram for SOURCE



Abbreviations: teze, tezepelumab; Q4W, once every 4 weeks.
[a] Informed consent received.
[b] Subjects who completed treatment and entered either the extension study or post-study follow-up.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The results of the quality assessments of each of the three pivotal trials (PATHWAY, NAVIGATOR, and SOURCE) are presented in Table 30.

The trials were well conducted and methodologically robust. Randomisation to tezepelumab or placebo was achieved via a central Interactive Web Response System (IWRS), and packaging and preparation of investigational products was undertaken by an independent product manager (e.g. a pharmacist or study nurse) to ensure all sponsor and investigational site staff were blinded with regard to the treatment administered.

PATHWAY was a Phase 2, randomised, double-blind, placebo-controlled dose-ranging study. Patients were appropriately randomised and demographics/characteristics were balanced between the trial arms. Staff administering the trial agents were unaware of trial arm assignments; however, it was unclear who was blinded across the entire study, despite it being described as double-blind. The study withdrawal rate was higher in the high dose tezepelumab arm than in the medium/low dose and placebo arms. Efficacy and safety analyses were conducted appropriately (Table 30).

NAVIGATOR was a Phase 3, randomised, double-blind, placebo-controlled study. Patients were appropriately randomised and demographics/characteristics were balanced between trial arms. All participants, sponsor staff, and investigational site staff were blinded. More patients discontinued treatment or the study in the placebo arm versus the tezepelumab arm. Efficacy and safety analyses were conducted appropriately and sensitivity analyses showed that missing data did not impact the overall result (Table 30).

SOURCE was a Phase 3, randomised, double-blind, placebo-controlled study. Patients were appropriately randomised and demographics/characteristics were balanced between the trial arms. All participants, sponsor staff, and investigational site staff were blinded. Study withdrawals were balanced between the trial arms. Efficacy and safety analyses were conducted appropriately and sensitivity analyses showed that missing data did not impact the overall result (Table 30).

B.2.5.1 Relevance of trial populations to patients in England

Subjects enrolled in the PATHWAY, NAVIGATOR, and SOURCE trials were broadly reflective of severe asthma patients seen in clinical practice in England (70, 73). The majority of enrolled subjects (~60%) were female, 50–60% had baseline EOS <300 cells/μL, and 40–75% had experienced two exacerbations in the 12 months prior to enrolment (see Section B.2.3.3).

While none of the randomised subjects PATHWAY, NAVIGATOR, and SOURCE were from the UK, subgroup analysis of the primary efficacy outcome in each trial suggested there was little to no effect of subject ethnicity or geographic region on tezepelumab treatment response.

Table 30: Quality assessment results for PATHWAY, NAVIGATOR, and SOURCE

Trial number (acronym)	PATHWAY (NCT02054130)	NAVIGATOR (NCT03347279)	SOURCE
Was randomisation carried out appropriately?	Yes. Patients were randomly assigned (1:1:1:1 ratio) according to a central interactive voice response or web-response system and stratified according to location, blood eosinophil count, and dose level of inhaled glucocorticoids.	Yes. Patients were randomly assigned in a 1:1 ratio via the interactive web response system/interactive voice response system. Patients were stratified according to location and age.	Yes. Patients were randomly assigned in a 1:1 ratio via an interactive web response system/interactive voice response system. Patients were stratified according to location.
Was the concealment of treatment allocation adequate?	Yes. Trial agents were similar in appearance and were administered by staff who were unaware of the trial group assignments.	Yes. The randomisation code was assigned from a randomisation list prepared by a computerised system.	Yes. The randomisation code was assigned from a randomisation list prepared by a computerised system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics and disease characteristics were balanced between the groups.	Yes. Demographics and disease characteristics were balanced between the groups.	Yes. Demographics and disease characteristics were balanced between the groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear. Study was reported as double-blind, but it was unclear who was blinded.	Yes. Study was reported as double-blind. All packaging and labelling of investigational product was done in such way as to ensure blinding for all sponsor and investigational site staff.	Yes. Study was reported as double-blind. All packaging and labelling of investigational product was done in such a way as to ensure blinding for subject and all sponsor and investigational site staff.
Were there any unexpected imbalances in drop-outs between groups?	Yes. Patient disposition indicates that more patients withdrew from high dose (n=22) compared with medium dose (n=15), low dose (n=11), and placebo (n=8).	Yes. Patient disposition indicates that more patients discontinued treatment in the placebo group (n=57) compared with tezepelumab (n=36). More patients discontinued the study in the placebo group (n=23) compared with the tezepelumab group (n=16).	No. Patient disposition indicated the overall drop-outs were generally well-balanced between treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the manuscript (by Corren 2017) all outcomes are reported in detail.	No. Based on the manuscript (by Menzies-Gow 2021) all outcomes are reported in detail.	No. Based on the clinical study report all outcomes are reported in detail.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate	Yes. Efficacy analyses were based on ITT analysis, defined as all randomised patients who received at least one dose of tezepelumab or placebo.	Yes. Efficacy analysis of the primary outcome was based on all randomised patients who received at least one dose of tezepelumab or placebo.	Yes. Efficacy analysis of the primary outcome was based all subjects randomised to study treatment who received at least one dose of

Trial number (acronym)	PATHWAY (NCT02054130)	NAVIGATOR (NCT03347279)	SOURCE
methods used to account for missing data?	The safety analysis set was defined as the as-treated population and included all the patients who received at least one dose of tezepelumab or placebo.	The safety analysis set was defined as the patients who received at least one dose of tezepelumab or placebo. Sensitivity analyses to assess the impact of missing data were performed and did not impact the overall result.	tezepelumab or placebo, irrespective of their protocol adherence and continued participation in the study. The safety analysis set was defined as all patients who received at least one dose of tezepelumab or placebo. For both analyses this was all patients randomised. Sensitivity analyses explored the effect of missing data on the reliability of the results using multiple imputation and determined that they did not affect the conclusions.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)			

Abbreviations: ITT, intent-to-treat.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 PATHWAY

SUMMARY

- In a broad population of adult subjects with severe, uncontrolled asthma, treatment with tezepelumab (any dose group) resulted in a significant reduction in the primary endpoint, AAER, compared with placebo at Week 52.
- At Week 52, AAER reductions of 62, 71, and 66% in the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab arms, respectively (compared with placebo) were observed in the ITT population (p<0.001).
- With all three tezepelumab doses, considerable improvements from baseline to Week 52 were observed for key secondary endpoints, including pre-BD FEV_1, ACQ-6, AQLQ(S)+12, and asthma symptom daily diary score, compared with placebo.

B.2.6.1.1 Primary efficacy outcome: AAER

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 asthma exacerbations over 52 weeks compared with placebo (Table 31). Numerically higher reductions in the exacerbation rate were observed with the two higher doses of tezepelumab (Please note that the tezepelumab 210 mg Q4W is the intended licensed dose).

Table 31: AAER over 52 weeks (ITT)

	Tezepelumab			Placebo (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	
AAER (95% CI)	0.27 (0.19, 0.38)	0.20 (0.13, 0.30)	0.23 (0.16, 0.34)	0.72 (0.59, 0.88)
Rate ratio (95% CI)	0.38 (0.23, 0.63)	0.29 (0.16, 0.51)	0.34 (0.20, 0.58)	-
p-value	<0.001	<0.001	<0.001	-

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; ICS, inhaled corticosteroids; ITT, intent-to-treat; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Rate = total number of asthma exacerbations in each group/total person-year follow-up in each group; 95% CI for rate was based on the exact 95% Poisson CI. Rate ratio and 95% CI for rate ratio were estimated from negative binomial regression with treatment group, and the stratification factors - baseline blood eosinophil count (≥ or < 250 cells/μL) and baseline ICS dose level (medium or high) as the covariates. A rate ratio <1 favoured tezepelumab. Nominal p-value was from the negative binomial regression based on pairwise comparisons against the placebo group.

B.2.6.1.2 Other efficacy outcomes

Results of the remaining efficacy outcomes of the Phase 2 PATHWAY trial are presented in Appendix L.

For secondary endpoints of lung function, including pre-bronchodilator (BD) FEV_1 and forced vital capacity (FVC), improvements from baseline were observed in all three tezepelumab dose arms compared with placebo at Week 52. Increases (indicating improvement) from baseline in pre-BD FEV_1 and FVC were observed as early as Week 4 (first time point assessed) in all three tezepelumab dose arms compared with placebo, and these increases were generally maintained over time for the duration of the study.

For the patient-reported outcomes, Asthma Control Questionnaire 6-item (ACQ-6), Asthma Quality of Life Questionnaire (Standardised) for 12 years and older (AQLQ(S)+12), and asthma symptom daily diary score, improvements from baseline were observed in all three tezepelumab dose groups compared with placebo at Week 52. Full details are provided in Appendix L.

B.2.6.2 NAVIGATOR

SUMMARY

In the Phase 3 NAVIGATOR trial, which enrolled a broad population of subjects with severe asthma, treatment with 210 mg tezepelumab SC Q4W resulted in statistically significant improvements over placebo in all primary and key secondary endpoints.

Compared with placebo, over the course of the 52-week study period, tezepelumab was shown to:

- Reduce AAER (the primary efficacy endpoint) by 56% (rate ratio: 0.44; 95% CI: 0.37, 0.53; p<0.001)
- Reduce the annualised rate of exacerbations associated with an ER visit or hospitalisation by 79% versus placebo (p<0.001)
- Reduce the annualised rate of exacerbations associated with a hospitalisation by 85% versus placebo (p<0.001)
- Improve FEV_1 at Week 52 by 0.13 L versus placebo (0.23 L versus 0.10 L; 95% CI: 0.08, 0.18; p<0.001)
    - Improvement in FEV_1 was observed at the first post-baseline time point it was assessed (2 weeks) and maintained to 52 weeks
- Improve patient QoL (AQLQ(S)+12), asthma control (ACQ-6), and asthma symptoms (ASD)
    - Improvements in each of these endpoints were observed at their first post-baseline assessment time points (between Weeks 1 and 4)

B.2.6.2.1 Primary efficacy outcome: AAER

Tezepelumab 210 mg SC Q4W treatment resulted in a clinically meaningful and statistically significant 56% reduction in the rate of asthma exacerbations over 52 weeks compared with placebo (rate ratio: 0.44 [95% CI: 0.37, 0.53]; p<0.001) (Table 32).

Table 32: AAER over 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
Number of events	[redacted]	[redacted]
Total time at-risk (years)	[redacted]	[redacted]
Crude rate	[redacted]	[redacted]
AAER (95% CI)	0.93 (0.80, 1.07)	2.10 (1.84, 2.39)
Absolute diff from placebo (95% CI)	[redacted]	
Rate ratio (95% CI)	0.44 (0.37, 0.53)	
p-value	<0.001	

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set.
A rate ratio <1 favoured tezepelumab. The overdispersion parameter was estimated to be 1.41. Model: 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 displayed are 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.

B.2.6.2.2 Key secondary outcome: Pre-BD FEV_1

Subjects treated with tezepelumab demonstrated a statistically significant and clinically meaningful improvement in pre-BD FEV_1 from baseline to 52 weeks compared with subjects treated with placebo (0.23 L versus 0.10 L; least squares [LS] mean difference: 0.13 L [95% CI: 0.08, 0.18]; p<0.001) (Table 33).

Onset of the effect of tezepelumab on FEV_1 was seen at the first post-baseline assessment at 2 weeks and was maintained over 52 weeks, as shown in Figure 13.

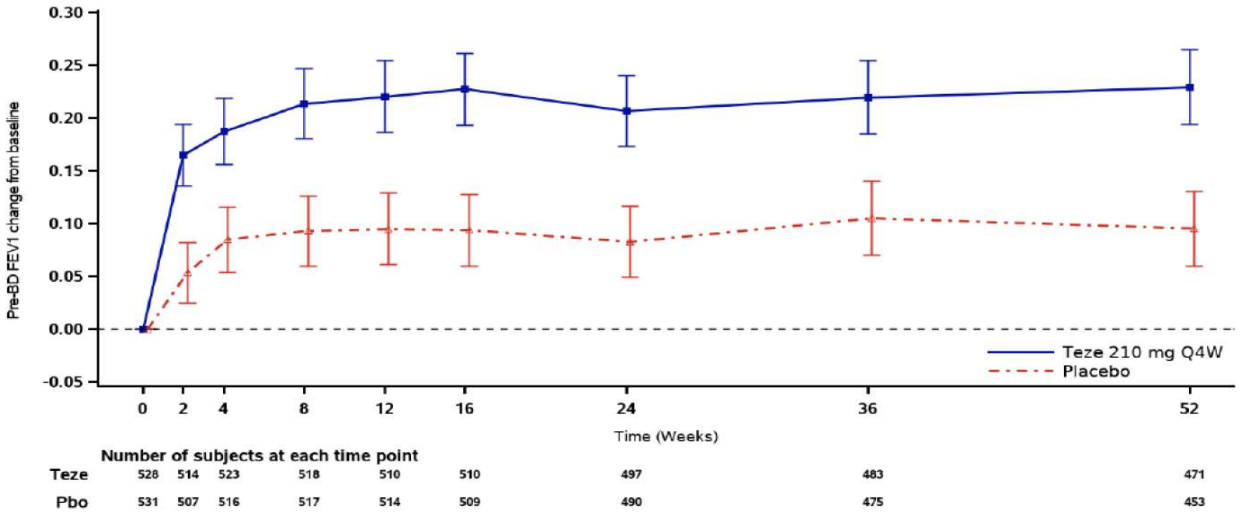
Table 33: pre-BD FEV_1 change from baseline at 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n1	[redacted]	[redacted]
n2	[redacted]	[redacted]
Change from baseline (L)	[redacted]	[redacted]
LS mean difference (95% CI)	0.13 (0.08, 0.18)	
p-value	<0.001	
Reject H0?	[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.

Baseline was 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 was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure was: Change from baseline in FEV_1 = Treatment group + region + age + baseline FEV_1 + visit + treatment * visit.

Figure 13: Adjusted mean (95% CI) change from baseline in pre-BD FEV_1 (FAS)



Abbreviations: BD, bronchodilator; CI, confidence interval; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; LS, least squares; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Baseline was 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 was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure was: Change from baseline in FEV_1 = Treatment group + region + age + baseline FEV1 + visit + treatment * visit.

B.2.6.2.3 Key secondary outcome: ACQ-6

Tezepelumab treatment resulted in a clinically meaningful improvement from baseline in ACQ-6, and a statistically significant improvement compared with placebo at 52 weeks (–1.53 versus –1.20, respectively; LS mean difference: –0.33 [95% CI: –0.46, –0.20]; p<0.001) (Table 34).

Table 34: ACQ-6 score change from baseline at 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
LS mean difference (95% CI)	–0.33 (–0.46, –0.20)	
p-value	<0.001	
Reject H0?	[redacted]	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CI, confidence interval; FAS, full analysis set; LS, least squares.
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.

In the responder analysis (a subject was classified as a responder if their change from baseline in ACQ-6 score was ≥0.5), a greater proportion of subjects in the tezepelumab arm achieved clinically meaningful improvements in ACQ-6 score compared with those in the placebo arm at Week 52 ([redacted] (Table 35).

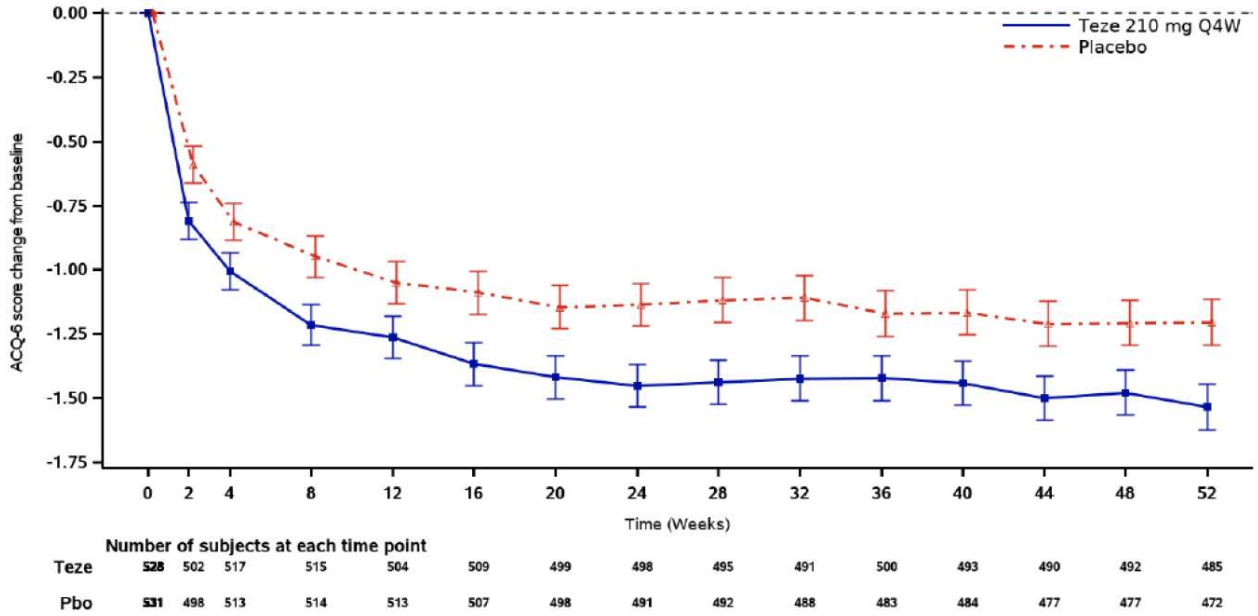
Improvements in ACQ-6 were seen as early as 2 weeks after administration and maintained to 52 weeks (Figure 14).

Table 35: GEE analysis of ACQ-6 responders (FAS)

Time point		Tezepelumab (n=528)	Placebo (n=531)
Week 4	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	
Week 12	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	
Week 52	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CI, confidence interval; FAS, full analysis set; GEE, generalised estimating equations; OR, odds ratio.
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.
† A subject was classified as a responder if their change from baseline in ACQ-6 score was ≥0.5.

Figure 14: Adjusted mean (95% CI) change from baseline in ACQ-6 score (FAS)



Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CI, confidence interval; FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. The model with unstructured covariance structure was: Change from baseline in ACQ-6 = Treatment group + region + age + baseline ACQ-6 + visit + treatment * visit.

B.2.6.2.4 Key secondary outcome: AQLQ(S)+12

Tezepelumab treatment resulted in a clinically meaningful improvement from baseline in AQLQ(S)+12, and a statistically significant improvement compared with placebo (1.48 versus 1.14, respectively; LS mean difference: 0.33 [95% CI: 0.20, 0.47]; p<0.001) (Table 36). An improvement from baseline was also observed in the placebo arm.

Table 36: AQLQ(S)+12 score change from baseline at 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
LS mean difference (95% CI)	0.33 (0.20, 0.47)	
p-value	<0.001	
Reject H0?	[redacted]	

Abbreviations: AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; CI, confidence interval; FAS, full analysis set; LS, least squares.
Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. AQLQ(S)+12 total score was defined as the unweighted mean of the responses to all questions in the questionnaire. If response to any of the questions was missing, the total score was missing. If a response to a question within a domain was missing, the score for that domain was missing. Estimate of the mean change from baseline at each week in tezepelumab was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure was: Change from baseline in AQLQ(S)+12 = Treatment group + region + age + baseline AQLQ(S)+12 + visit + treatment * visit.

In the responder analysis (a subject was classified as a responder if their change from baseline in AQLQ(S)+12 total score was ≥0.5), a greater proportion of subjects in the tezepelumab arm achieved clinically meaningful improvements in AQLQ(S)+12 score compared with those in the placebo arm at Week 52 [redacted] (Table 37).

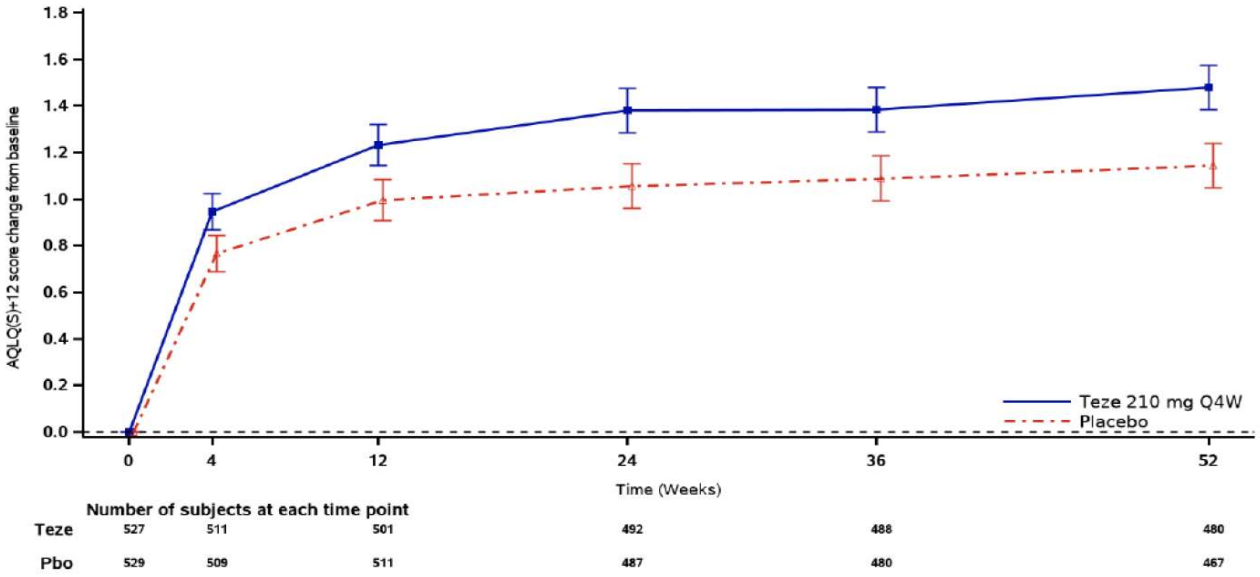
Improvements in AQLQ(S)+12 were seen as early as 4 weeks after administration (the first time point at which AQLQ(S)+12 was assessed) and maintained to 52 weeks (Figure 15).

Table 37: GEE analysis of AQLQ(S)+12 responders (FAS)

Time point		Tezepelumab (n=528)	Placebo (n=531)
Week 4	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	
Week 12	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	
Week 52	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	OR (95% CI)	[redacted]	
	p-value	[redacted]	

Abbreviations: AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; CI, confidence interval; FAS, full analysis set; GEE, generalised estimating equations; OR, odds ratio.
AQLQ(S)+12 total score was defined as the unweighted mean of the responses to all questions in the questionnaire. If response to any of the questions was missing, the total score 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 AQLQ(S)+12 score as covariates. Unadjusted CI and nominal p-values are presented, as analysis was not included in the multiple testing procedure.
† A subject was classified as a responder if their change from baseline in AQLQ(S)+12 total score was ≥0.5.

Figure 15: Adjusted mean (95% CI) change from baseline in AQLQ(S)+12 total score (FAS)



Abbreviations: AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; CI, confidence interval; FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. The model with unstructured covariance structure was: Change from baseline in AQLQ(S)+12 = Treatment group + region + age + baseline AQLQ(S)+12 + visit + treatment * visit.

B.2.6.2.5 Key secondary outcome: Asthma Symptom Diary (ASD) score (Weekly Mean Daily Score)

Tezepelumab treatment resulted in clinically meaningful improvements from baseline in ASD score and a statistically significant improvement compared with placebo at 52 weeks (–0.70 versus –0.59, respectively; LS mean difference: –0.11 [95% CI: –0.19, –0.04]; p=0.004) (Table 38).

Table 38: ASD† score change from baseline at 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
LS mean difference (95% CI)	–0.11 (–0.19, –0.04)	
p-value	0.004	
Reject H0?	[redacted]	

Abbreviations: ASD, Asthma Symptom Diary; CI, confidence interval; FAS, full analysis set; LS, least squares.
Baseline was defined as the mean of the available data in the most recent week prior to the date of randomisation. Each period was defined from the evening of the first day (1 week prior to the time point displayed) to the morning of the last day (at the time point displayed). If more than 3 days were missing within a week, then the weekly mean was set to missing. No imputation was made for missing values. Estimate of the mean change from baseline at each week in tezepelumab was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with First Order Regressive covariance structure was: Change from baseline in Asthma Symptom Diary score = Treatment group + region + age + baseline Asthma Score + week + treatment * week.
† Completed by subjects twice daily. The ASD consists of 10 items. Five morning items assess night-time symptom severity in relation to: wheezing, shortness of breath, cough, chest tightness, and the frequency of night-time awakening. Five evening items assess daytime symptom severity in relation to: wheezing, shortness of breath, cough, chest tightness, and activity limitation since waking (6).

In the responder analysis (a subject was classified as a responder if their change from baseline in ASD was ≥0.5), a greater proportion of subjects in the tezepelumab arm achieved clinically meaningful improvements in ASD score compared with those in the placebo arm at Week 52 [redacted] (Table 39).

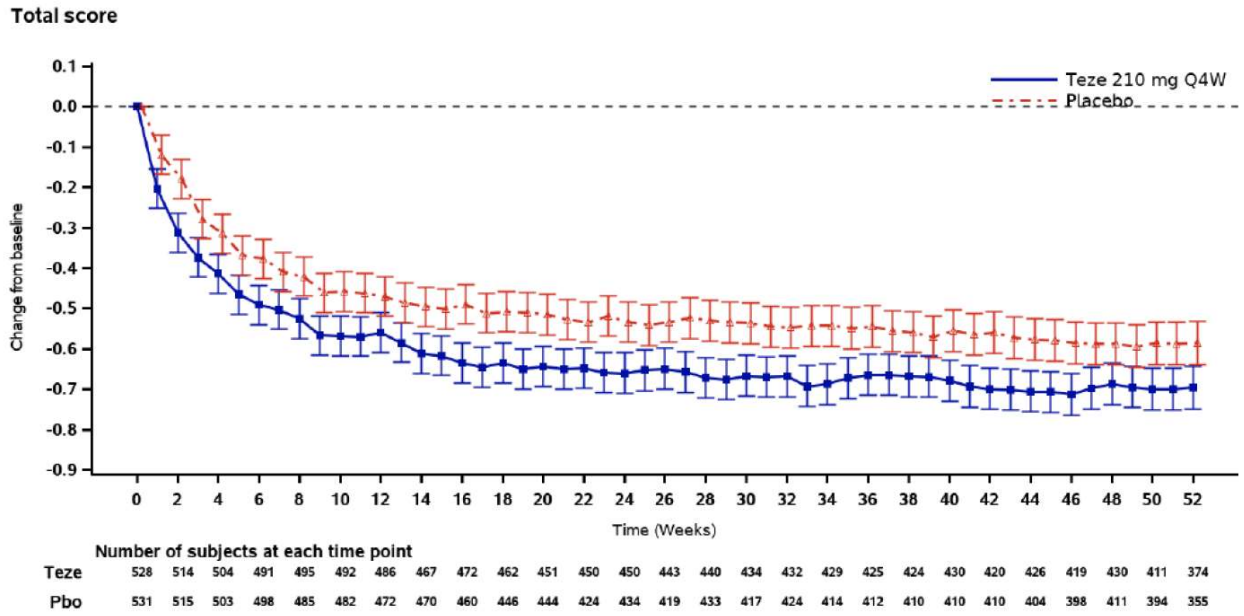
Improvements in ASD score were seen as early as 2 weeks after administration and maintained to 52 weeks (Figure 16).

Table 39: ASD score responders by time point (FAS)

Time point		Tezepelumab (n=528)	Placebo (n=531)
Week 1	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	Non-responder, n (%)	[redacted]	[redacted]
Week 52	n	[redacted]	[redacted]
	Responders, n (%)†	[redacted]	[redacted]
	Non-responder, n (%)	[redacted]	[redacted]

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; FAS, full analysis set.
Baseline was defined as the mean of the available ASD scores in the most recent week prior to the date of randomisation. Calculation of percentages was based on the number of subjects in the FAS with a completed assessment at each time point.
† A subject was classified as a responder if their change from baseline in weekly ASD total score was ≥–0.5.

Figure 16: Adjusted mean (95% CI) change from baseline in ASD score (FAS)



Abbreviations: ASD, Asthma Symptom Diary score; CI, confidence interval; FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Baseline was defined as the mean of the available data in the most recent week prior to the date of randomisation. The model, First Order Regressive covariance structure, was: Change from baseline in Asthma Symptom Diary score = Treatment group + region + age + baseline Asthma Score + week + treatment * week.

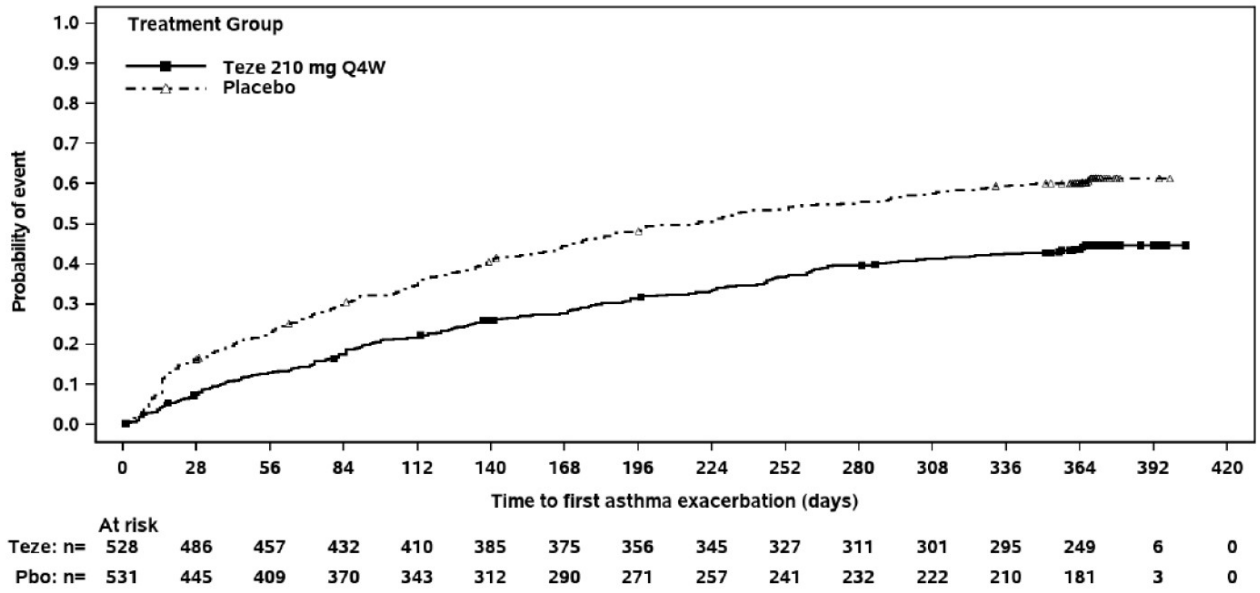
B.2.6.2.6 Other secondary efficacy outcomes

The below section includes other secondary efficacy outcomes that inform the model. Additional secondary efficacy outcomes that do not inform the model are presented in Appendix M.

Time to first asthma exacerbation

- The time to first exacerbation was nominally statistically significantly longer in the tezepelumab versus the placebo arm (HR: [redacted]), as shown in Figure 17.

Figure 17: Time to first asthma exacerbation (Kaplan–Meier plot; FAS)



Abbreviations: FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Time to first exacerbation was calculated as date of first asthma exacerbation - date of randomisation + 1. Subjects with no observed event (asthma exacerbation) were censored at the end of the time at risk. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation could not occur, were not included in the calculation of time at risk for exacerbation. Censoring symbols indicate time when a subject completed planned treatment or withdrew from study during planned treatment without an asthma exacerbation.

Proportion of subjects experiencing no asthma exacerbations over 52 weeks

- A [redacted]

Annualised rate of exacerbations associated with ER visit or hospitalisation

Compared with placebo, tezepelumab treatment resulted in a [redacted] in the annualised rate of exacerbations associated with an

ER visit or hospitalisation, and an [redacted], as shown in Table 40

- The proportion of subjects followed for 52 weeks and who did not experience an asthma exacerbation requiring an ER visit or hospitalisation was [redacted]

Table 40: Annual exacerbations associated with an ER visit or hospitalisation over 52 weeks (FAS)

		Tezepelumab (n=528)	Placebo (n=531)
Annual exacerbations associated with an ER visit or hospitalisation†	n	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	Total time at-risk, years	[redacted]	[redacted]
	Crude rate	[redacted]	[redacted]
	AAER (95% CI)	[redacted]	[redacted]
	Absolute diff from placebo (95% CI)	[redacted]	
	Rate ratio (95% CI)	[redacted]	
	p-value	[redacted]	
Annual exacerbations associated with a hospitalisation‡	n	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	Total time at-risk, years	[redacted]	[redacted]
	Crude rate	[redacted]	[redacted]
	AAER (95% CI)	[redacted]	[redacted]
	Absolute diff from placebo (95% CI)	[redacted]	
	Rate ratio (95% CI)	[redacted]	
	p-value	[redacted]	

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; ER, emergency room; FAS, full analysis set.
A rate ratio <1 favoured tezepelumab. Model: 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 displayed are 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. Unadjusted CI and Nominal p-value are presented, as the analysis was not included in the multiple testing procedure. Exacerbations associated with hospitalisations and ER visits that were adjudicated not to be asthma related were removed; hospitalisations and ER visits that were adjudicated to be due to an asthma exacerbation were added.
† The overdispersion parameter was estimated to be 7.48.
‡ The overdispersion parameter was estimated to be 11.63.

EQ-5D-5L

- Improvements in the current HRQoL of subjects treated with tezepelumab were observed at after Week 10, compared with placebo, as measured by EQ-5D-5L (Table 41)

- Tezepelumab treatment improved scores and increased the percentage of subjects [redacted] at Week 52 compared with placebo

Table 41: EQ-5D-5L score change from baseline at 52 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n	[redacted]	[redacted]
LS mean (SE) change from baseline to Week 52	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; FAS, full analysis set; LS, least squares; SE, standard error.
Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. The Health State Valuation (an index-based value) for the EQ-5D-5L was derived from the five dimensions using the UK population-based preference weights. Estimate of the mean change from baseline at each week in tezepelumab was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure was: Change from baseline in HSV index = Treatment group + region + age + baseline HSV index + visit + treatment * visit.

B.2.6.2.7 Conclusion

- The NAVIGATOR trial achieved its primary efficacy endpoint, demonstrating a statistically significant (and clinically meaningful) 56% reduction in the annualised asthma exacerbation rate (AAER) with tezepelumab versus placebo in the enrolled broad population of adults and adolescents with severe uncontrolled asthma
- Clinically meaningful reductions in exacerbations with tezepelumab treatment were observed irrespective of subject baseline levels of EOS, FeNO, or IgE, or baseline allergic/non-allergic status (see Section B.2.7.1.2)
- Tezepelumab treatment resulted in statistically significant and clinically meaningful improvements in lung function (pre-BD FEV_1) versus placebo, with improvements seen by 2 weeks (the earliest time point assessed) and sustained to 52 weeks
- Tezepelumab treatment also resulted in clinically meaningful improvements from baseline in quality of life (AQLQ[S]+12), asthma control (ACQ-6), and asthma symptoms (ASD) that were statistically significant compared with placebo, with an onset of effect as early as the first assessment (between Week 1 and 4) and maintained to 52 weeks

B.2.6.3 SOURCE

SUMMARY

- For the primary efficacy endpoint, the odds of reaching a category of greater percent mOCS reduction were numerically higher with tezepelumab 210 mg Q4W treatment versus placebo, with a cumulative OR of 1.28 (95% CI: 0.69, 2.35, p=0.434), but was not statistically significant
- A total of [redacted] of subjects in the tezepelumab arm ([redacted] in the placebo arm) achieved a ≥90 to ≤100% reduction in mOCS dose at Week 48 without losing asthma control
- In addition, at Week 48, tezepelumab treatment also resulted in:
  - A [redacted] in AAER compared with placebo
  - A [redacted] from baseline in pre-BD FEV_1, compared with placebo
  - [redacted] for the PROs of ASD, ACQ-6, and AQLQ(S)+12 scores compared with placebo
- Overall, efficacy results from SOURCE support observations from NAVIGATOR and PATHWAY in relation to the benefits of tezepelumab on exacerbations, lung function, and asthma control in mOCS-dependent patients, despite a considerable reduction in daily mOCS dose
- By preventing exacerbations, tezepelumab prevents patients from requiring either short bursts or chronic OCS use, reduces the need for OCS in OCS-dependent patients and demonstrates clinically meaningful improvements in key outcomes for OCS-dependent patients

B.2.6.3.1 Primary efficacy outcome: Categorised percent reduction in daily OCS dose while not losing asthma control

Results from the SOURCE trial favoured tezepelumab 210 mg SC Q4W over placebo, but the primary endpoint (categorised percent reduction in the daily OCS dose without loss of asthma control at Week 48 with tezepelumab plus standard of care compared with placebo plus standard of care) did not reach statistical significance and hence was not met (Section B.2.13.2.1 discusses the reasons why statistical significance was not met). The odds of reaching a category of greater percent OCS reduction was numerically higher with tezepelumab versus placebo, with a cumulative OR of 1.28 (95% CI: 0.69, 2.35; p=0.434) but was not statistically significant (Figure 18 and Table 42).

The proportion of subjects achieving a ≥90 to ≤100% reduction in mOCS dose at Week 48 without losing asthma control was 54.1% in the tezepelumab group and 46.1% in the placebo group.

Figure 18: Proportion of subjects in different categories of reduction from baseline in final daily OCS dose at Week 48 (FAS)

Abbreviations: AI, adrenal insufficiency; FAS, full analysis set; OCS, oral corticosteroid; Q4W, once every 4 weeks; teze, tezepelumab.
Derivation of daily OCS dose included a therapy reason of “asthma maintenance dose”, “titration, due to asthma”, and “other: AI”.

Table 42: Percent reduction from baseline in final daily OCS dose at Week 48 (FAS)

	Tezepelumab [redacted]	Placebo [redacted]
Reduction from baseline in final daily OCS dose, n (%)		
≥90 to ≤100%	[redacted]	[redacted]
≥75 to <90%	[redacted]	[redacted]
≥50 to <75%	[redacted]	[redacted]
>0 to <50%	[redacted]	[redacted]
No change or any increase	[redacted]	[redacted]
Comparison between treatment groups		
Cumulative OR (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: AI, adrenal insufficiency; CI, confidence interval; OCS, oral corticosteroid; OR, odds ratio; Q4W, once every 4 weeks; SAP, statistical analysis plan.
Baseline daily OCS dose was defined based on the prescribed dose per day at Visit 6. Final daily OCS dose was defined based on the prescribed dose per day at end of treatment visit. Derivation of daily OCS dose included a therapy reason of “asthma maintenance dose”, “titration, due to asthma”, and “Other: AI.” The estimate of the cumulative OR was obtained using a proportion odds model with treatment, region, and daily OCS dose at baseline as covariates.

The mean change from baseline in daily OCS dose over time is presented in Figure 19. The separation of the curves was evident from Week 4 onwards.

Figure 19: Mean (± 1 SE) percentage change from baseline in daily OCS dose over time (FAS)

Abbreviation: AI, adrenal insufficiency; CI, confidence interval; FAS, full analysis set; OCS, oral corticosteroid; Pbo, placebo; Q4W, once every 4 weeks; SE, standard error; Teze, tezepelumab.
Means +/- one standard error are presented. Derivation of daily OCS dose included a therapy reason of "asthma maintenance dose", "titration, due to asthma", and "Other: AI."

Subjects in the tezepelumab arm had a [redacted] compared with those in the placebo arm at Week 48, as shown in Table 43 and Figure 20.

Table 43: Percent reduction from baseline in final daily OCS dose at Week 48; van Elteren Test (FAS)

	Tezepelumab [redacted]	Placebo [redacted]
Median (95% CI)	[redacted]	[redacted]
Median difference (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: AI, adrenal insufficiency; CI, confidence interval; FAS, full analysis set; OCS, oral corticosteroid.
Baseline daily OCS dose was defined based on the prescribed dose per day at Visit 6. Final daily OCS dose was defined based on the prescribed dose per day at end of treatment visit. Derivation of daily OCS dose included a therapy reason of "asthma maintenance dose", "titration, due to asthma", and "Other: AI." The CIs for the median in each treatment group were estimated using a distribution free procedure. The median difference in the percentage reduction of daily OCS dose between the tezepelumab and placebo arms and their respective 95% CIs were derived using an unadjusted bootstrap approach. The p-value was obtained using a Wilcoxon rank sum test stratified by region (van Elteren). The response variable was the percentage reduction from baseline in final daily OCS dose at Week 48.

Figure 20: Median (95% CI) percentage change from baseline in daily OCS dose over time (FAS)

Abbreviations: AI, adrenal insufficiency; CI, confidence interval; FAS, full analysis set; OCS, oral corticosteroid; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
CIs were calculated using a distribution free procedure. Derivation of OCS dose included a therapy reason of "asthma maintenance dose," "titration, due to asthma," and "other: AI."

B.2.6.3.2 Key secondary outcome: AAER

Since the primary efficacy endpoint of SOURCE was not met (for the reasons described in Section B.2.13.2.1), the key secondary endpoint of SOURCE was not formally assessed. Subjects treated with tezepelumab

. Tezepelumab treatment reduced the rate of exacerbations by compared with placebo in subjects with mOCS-dependent severe asthma, despite the reductions in mOCS use (Table 44).

Table 44: AAER over 48 weeks (FAS)

	Tezepelumab	Placebo
Number of events		
Total time at-risk (years)		
Crude rate		
AAER (95% CI)		
Absolute diff from placebo (95% CI)		
Rate ratio (95% CI)		
p-value		

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set; Q4W, once every 4 weeks.
The overdispersion parameter was estimated to be 1.16. A rate ratio <1 favoured tezepelumab. Model: A negative binomial regression analysis with treatment, region, and history of exacerbations as covariates. The logarithm of the time at risk was used as an offset variable. Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences are estimated via the delta method.

B.2.6.3.3 Other secondary efficacy outcomes relevant to model and/or scope

The below section includes other secondary efficacy outcomes that inform the model. Additional secondary efficacy outcomes that do not inform the model are presented in Appendix N.

Time to first asthma exacerbation

- The Kaplan–Meier plot of time to first exacerbation is presented in Figure 21.

[redacted])

Figure 21: Time to first asthma exacerbation (Kaplan–Meier plot; FAS)

Abbreviations: FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; teze, tezepelumab.
Time to first exacerbation was calculated as start date of the first asthma exacerbation – date of randomisation + 1. Subjects with no observed event (asthma exacerbation) were censored at the end of the time at risk. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation could not occur, were not included in the calculation of time at risk for exacerbation. Censoring symbols indicate time when a subject completed planned treatment or withdrew from the study during the planned treatment without an asthma exacerbation.

Annualised rate of exacerbations associated with ER visit or hospitalisation

- The numbers of exacerbations in the SOURCE study resulting in an ER visit or hospitalisation [redacted]
- Subjects taking tezepelumab had a [redacted] in exacerbations requiring hospitalisation or an ER visit when compared with placebo, despite the reduction in mOCS dose [redacted] (Table 45)

Table 45: Annual exacerbations associated with an ER visit or hospitalisation over 48 weeks (FAS)

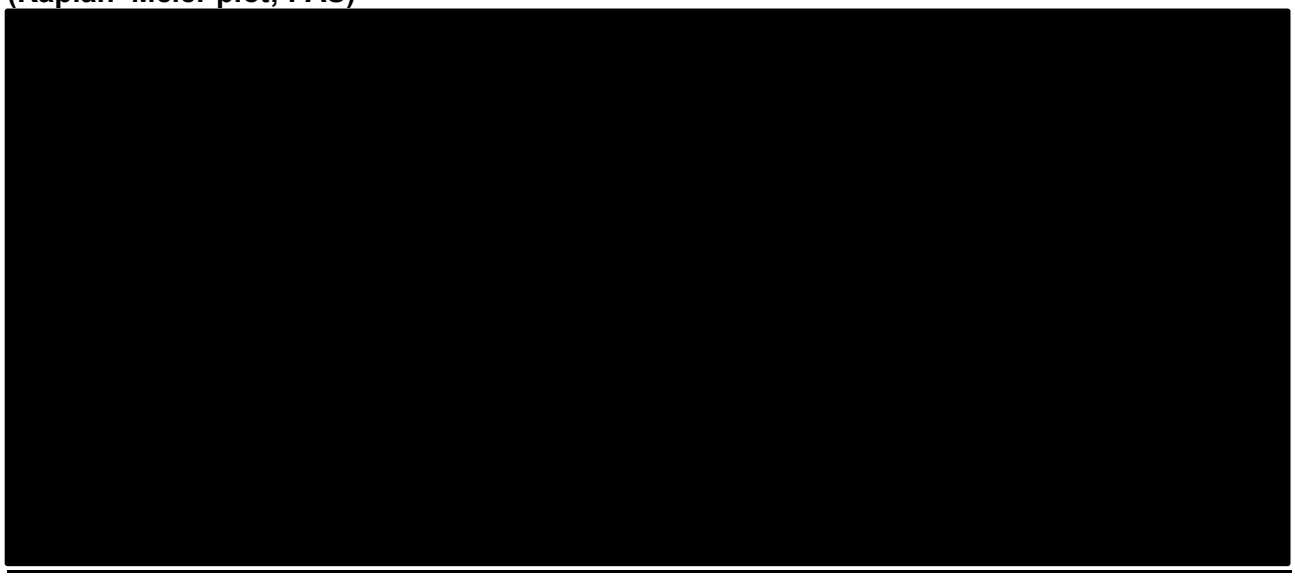
	Tezepelumab [redacted]	Placebo [redacted]
n	[redacted]	[redacted]
Number of events	[redacted]	[redacted]
Total time at-risk, years	[redacted]	[redacted]
Crude rate	[redacted]	[redacted]
AER (95% CI)	[redacted]	[redacted]
Absolute diff from placebo (95% CI)	[redacted]	
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: AER, annual exacerbation rate; CI, confidence interval; ER, emergency room; FAS, full analysis set.
The overdispersion parameter was estimated to be 3.52. A rate ratio <1 favoured tezepelumab.
Model: a negative binomial regression analysis with treatment, region, and history of exacerbations as covariates. The logarithm of the time at risk was used as an offset variable. 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.

Time to first asthma exacerbation associated with ER visit or hospitalisation

- The Kaplan–Meier plot for time to first asthma exacerbation associated with an ER visit or hospitalisation is presented in Figure 22.
- The risk of having an exacerbation leading to an ER visit or hospitalisation was numerically lower for subjects receiving tezepelumab than those receiving placebo, despite the reduction in mOCS dose, although the number of events was low ([redacted]

Figure 22: Time to first asthma exacerbation associated with ER visit or hospitalisation (Kaplan–Meier plot; FAS)



Abbreviations: ER, emergency room; FAS, full analysis set; Pbo, placebo; Q4W, once every 4 weeks; SCS, systemic corticosteroid; teze, tezepelumab.
Time to first exacerbation associated with ER visit or hospitalisation was calculated as the start date of the first asthma

exacerbation associated with ER visit or hospitalisation – date of randomisation + 1. Subjects with no observed event (asthma exacerbation due to ER visit or hospitalisation) were censored at the end of the time at risk. The time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation could not occur, were not included in the calculation of time at risk for exacerbation. An ER visit due to asthma required SCS bolus for at least 3 consecutive days or a single depot-injectable dose of corticosteroids. Censoring symbols indicate time when a subject completed planned treatment or withdrew from the study during the planned treatment without an asthma exacerbation associated with an ER visit or hospitalisation.

Proportion of subjects experiencing no asthma exacerbations over 48 weeks

- A numerically higher proportion of subjects in the tezepelumab arm (47.3%) did not experience an asthma exacerbation between baseline and Week 48 compared with 34.2% of subjects in the placebo arm (OR: 1.68 [95% CI: 0.85, 3.31]; p=0.133)

Proportion of subjects with reduction in final mOCS dose

- The potential for tezepelumab to allow reduction of daily mOCS dose at Week 48 was assessed in multiple secondary endpoints (Table 46). No meaningful difference was observed between treatment groups. Only one subject could not reduce final mOCS dose by 100% due to adrenal insufficiency

Table 46: Proportion of subjects with reduction from baseline in final daily OCS dose at Week 48 (FAS)

Endpoint	Tezepelumab (n=74)	Placebo (n=76)
100% reduction from baseline in daily OCS dose		
n (%)	40 (54.1)	35 (46.1)
OR (95% CI)	1.35 (0.68, 2.68)	
p-value	0.385	
≥50% reduction from baseline in daily OCS dose		
n (%)	55 (74.3)	53 (69.7)
OR (95% CI)	1.24 (0.60, 2.57)	
p-value	0.559	
Final daily OCS dose of ≤5 mg		
n (%)	53 (71.6)	55 (72.4)
OR (95% CI)	0.88 (0.40, 1.94)	
p-value	0.745	
Final daily OCS dose of ≤5 mg and unable to achieve 100% reduction due to AI		
n (%)	1 (1.4)	0 (0.0)
OR (95% CI)	ND	
p-value	ND	
Final daily OCS dose of ≤5 mg and unable to achieve 100% reduction due to AI and subjects with 100% reduction in final daily OCS dose		
n (%)	41 (55.4)	35 (46.1)
OR (95% CI)	1.44 (0.73, 2.86)	

Endpoint	Tezepelumab (n=74)	Placebo (n=76)
p-value	0.296	

Abbreviations: AI, adrenal insufficiency; CI, confidence interval; FAS, full analysis set; ND, not determined; OCS, oral corticosteroid; OR, odds ratio; Q4W, once every 4 weeks.
Baseline daily OCS dose was defined based on the prescribed dose per day at Visit 6. Final daily OCS dose was defined based on the prescribed dose per day at end of treatment visit.
Derivation of daily OCS dose included a therapy reason of "asthma maintenance dose", "titration, due to asthma", and "Other: AI." An OR greater than 1 favoured tezepelumab. The estimate of the OR was obtained using a logistic regression model with treatment, region, and daily OCS dose at baseline as covariates.

ASD

- Compared with placebo, subjects who received tezepelumab had a numerically greater improvement in ASD total score from baseline at Week 48 (LS mean difference: –0.10 [95% CI: –0.29, 0.09]), with the difference apparent during the initial 4-week induction period (Week 0–4)
- A numerically greater number of subjects treated with tezepelumab had a clinically meaningful improvement in ASD score from baseline to Week 48 compared with placebo (proportion of responders: 43.1 vs 29.4%; OR: 8.98 [95% CI: 0.63, 127.41])
- Fewer symptomatic days were reported in the tezepelumab arm versus the placebo arm over 48 weeks (change from baseline: –27.94 versus –6.60, respectively)

ACQ-6

- A clinically meaningful change in ACQ-6 from baseline to Week 48 was observed in both the tezepelumab and placebo groups and the improvement from baseline was greater with tezepelumab than with placebo (LS mean difference: –0.37; [95% CI: –0.71, –0.02])
- In the tezepelumab group, more patients achieved a clinically meaningful improvement in ACQ-6 (defined as ≥0.5 unit reduction from baseline) compared with placebo at Week 48 (65.2 vs 45.6%; OR: 2.30 [95% CI: 1.10, 4.81])
- More patients in the tezepelumab group achieved asthma control (ACQ-6 score ≤0.75) compared with placebo at Week 48 (30.3 vs 14.7%)

AQLQ(S)+12

- A clinically meaningful change in ALQ(S)+12 from baseline to Week 48 was observed in the tezepelumab and placebo groups and was greater in the tezepelumab group, with a total score LS mean change of 0.94 and 0.58 for tezepelumab and placebo, respectively (LS mean difference: 0.36 [95% CI 0.01, 0.70])

- All domain score changes were greater in the tezepelumab group than the placebo group and the onset of effect was evident from Week 4 (first timepoint of AQLQ(S)+12 assessment)

EQ-5D-5L

- Subjects treated with tezepelumab had a greater improvement in EQ-5D-5L visual analogue scale scores versus placebo (LS mean difference: 7.21 [95% CI 1,01, 13.41]) (Table 47)

Table 47: EQ-5D-5L score change from baseline at 48 weeks (FAS)

	Tezepelumab (n=528)	Placebo (n=531)
n	62	58
LS mean (SE) change from baseline to Week 52	9.21 (2.209)	2.00 (2.226)
LS mean difference (95% CI)	7.21 (1.01, 13.41)	
p-value	0.023	

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; FAS, full analysis set; LS, least squares; SE, standard error.
Baseline was defined as the last non-missing measurement recorded on or prior to randomisation. The Visual Analog Scale is a scale of 0–100 where subjects rate current health status, with 0 being the worst imaginable health state. Estimate of the mean change from baseline at each week in tezepelumab was compared with placebo using a repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure was: Change from baseline in VAS = Treatment group + region + baseline VAS + visit + treatment * visit.

Asthma-specific resource utilisation

- There was no meaningful difference between treatment groups in asthma-specific resource utilisation at Week 48
- The most common healthcare utilisation was ‘visit to specialist’ with a mean (SD) number of visits at baseline of 4.0 (4.1) and 4.8 (5.5) for tezepelumab and placebo, respectively and 1.0 (1.6) and 1.4 (2.1) at Week 48

B.2.6.3.4 Conclusion

Overall, efficacy results from SOURCE support observations from NAVIGATOR and PATHWAY in relation to the benefits of tezepelumab on exacerbations, lung function, and asthma control in mOCS-dependent patients, despite a considerable reduction in daily mOCS dose. SOURCE showed numerical benefits with tezepelumab treatment across secondary endpoints, including AAER, FEV_1, and the PROs ASD, ACQ-6, and AQLQ(S)+12, while subjects were reducing their maintenance OCS dose.

By preventing exacerbations, tezepelumab prevents patients from requiring either short bursts or chronic OCS use, reduces the need for OCS in OCS-dependent patients and

demonstrates clinically meaningful improvements in key outcomes for OCS-dependent patients.

Although SOURCE did not meet its primary endpoint, it did demonstrate a numerical improvement in the odds of achieving a categorical reduction in mOCS dose with tezepelumab treatment versus placebo.

The placebo response seen in the SOURCE trial was larger than expected and may be attributable to the trial design which had a long duration of the OCS reduction phase (36 weeks versus 16-20 weeks in other similar studies) and allowed multiple down titration attempts in the reduction phase. The placebo response suggests that some patients recruited may have been on OCS unnecessarily and were able to withdraw without a loss of control. These assumptions as to why SOURCE failed to reach significance have been validated with UK clinicians who commented that the trial design inadvertently introduced risk to achieving the primary endpoint and that in the real world, they would expect to see OCS sparing as a result of tezepelumab treatment in line with other biologics (96). A more detailed explanation of the data limitations of SOURCE are found in Section B.3.11.

B.2.7 Subgroup analyses

B.2.7.1 Pre-specified subgroup analyses

B.2.7.1.1 PATHWAY

Asthma exacerbation rate reduction (AERR) by pre-specified subgroups

- All three doses of tezepelumab reduced the rate of asthma exacerbations versus placebo over 52 weeks in the analysed subgroups, including blood EOS, FeNO, and Th2 status. The forest plot for the tezepelumab 210 mg dose arm (the intended licensed dose) is presented in Figure 23.

Figure 23: AERR over 52 weeks by pre-planned subgroups (ITT): Tezepelumab 210 mg Q4W

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.

B.2.7.1.2 NAVIGATOR

AAER reduction by baseline biomarkers and other characteristics

Subgroups of subjects based on baseline biomarkers and other characteristics showed broadly consistent AAER results as that seen in the overall analysis using the broad patient population. In subgroup analysis, tezepelumab treatment reduced the rate of asthma exacerbations versus placebo over 52 weeks, irrespective of the baseline levels of blood EOS, FeNO, total IgE, or perennial aeroallergen-specific IgE status at baseline when analysed categorically or along a continuum, and irrespective of other baseline characteristics.

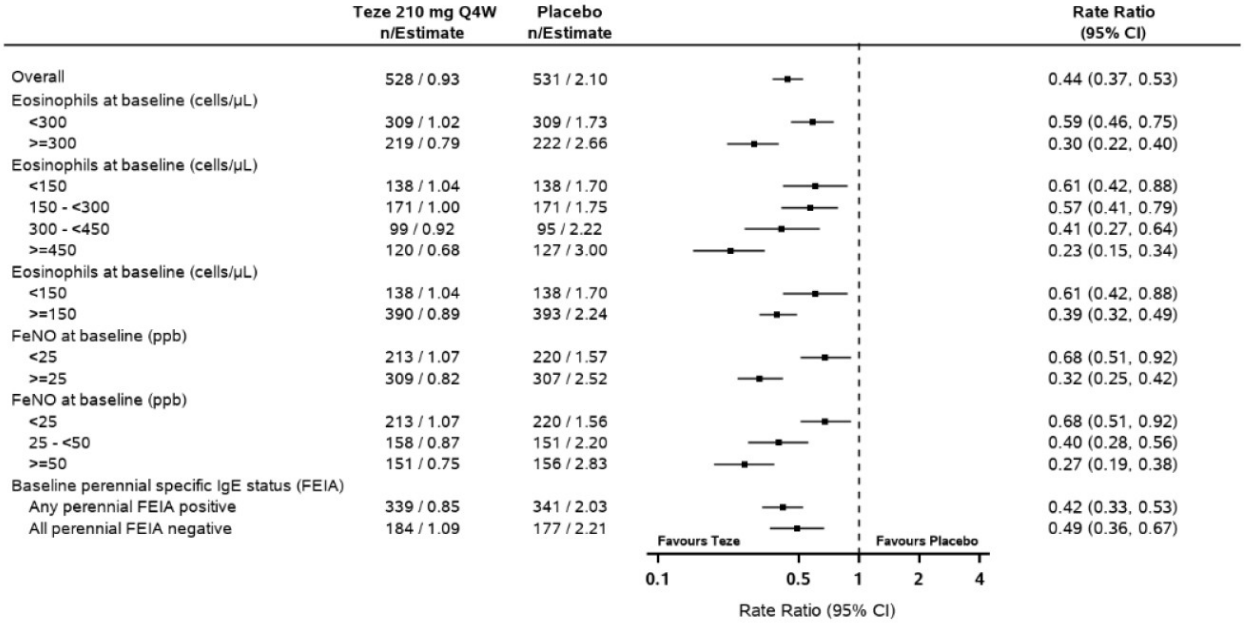
AAER reduction by categorical baseline biomarkers

As shown in Figure 24, compared with placebo, tezepelumab treatment reduced AAER by:

- 39% in subjects with baseline blood EOS <150 cells/μL
- 41% in subjects with baseline blood EOS <300 cells/μL
- 70% in subjects with baseline blood EOS ≥300 cells/μL

The benefit of tezepelumab over placebo in reducing AAER was similar in subjects with or without any positive baseline perennial aeroallergen-specific IgE FEIA result (Figure 24). Not shown in Figure 24, tezepelumab also reduced AAER in subjects irrespective of their baseline serum IgE levels. In the placebo arm, AAER increased with increasing baseline blood EOS count and FeNO levels.

Figure 24: AAER ratio over 52 weeks by baseline biomarker subgroup (FAS)

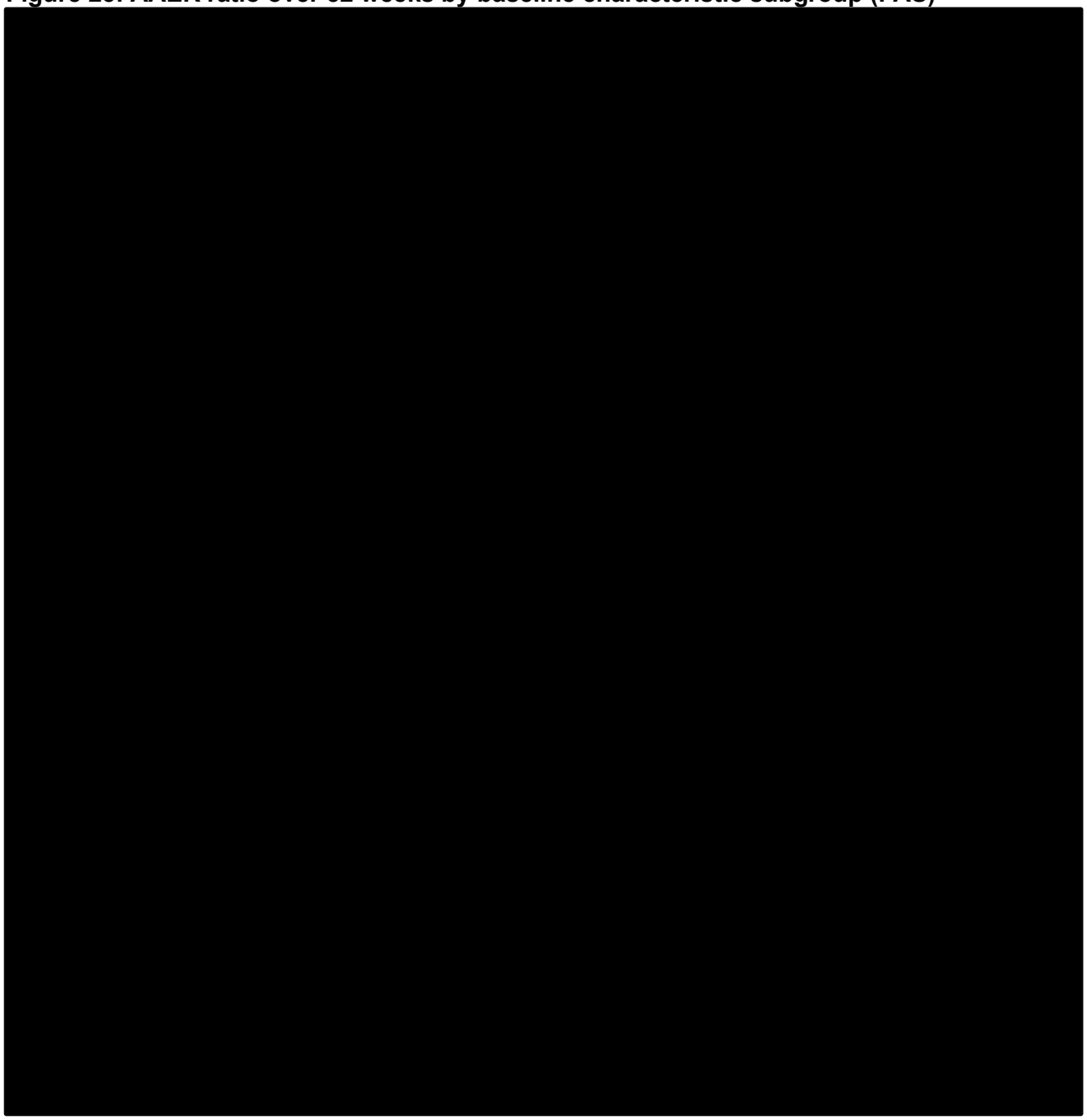


Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; teze, tezepelumab; Q4W, once every 4 weeks.
Rate ratio is displayed on the log scale. The dotted 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.

AAER reduction by baseline characteristics

As shown in Figure 25, tezepelumab treatment resulted in clinically meaningful reductions in AAER across most subgroups, including by baseline ICS dose, age, sex, race, [redacted]), OCS use, [redacted] geographic region (excluding Central/Eastern Europe), and nasal polyps in the 2 years before randomisation. Due to small numbers of subjects in certain subgroups, however (adolescents, Black or African American race, "Other" race, OCS present at baseline, and Central/Eastern Europe geography), the CIs for these subgroups did not exclude one. [redacted].

Figure 25: AAER ratio over 52 weeks by baseline characteristic subgroup (FAS)



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.

B.2.7.1.3 SOURCE

OCS dose reduction by pre-specified subgroups

The results for the primary efficacy endpoint in SOURCE (OCS dose reduction) were [redacted] the pre-planned baseline characteristic subgroup analyses as shown in Figure 26. The odds ratio point estimates

[redacted]). [redacted]. Although these analyses of the primary endpoint were pre-specified, due to the small number of subjects, these results should be interpreted with caution.

Figure 26: Categorised percent reduction in daily OCS dose at Week 48 by baseline characteristic subgroup (FAS)

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.

B.2.7.2 Post hoc subgroup analyses

In order to inform the stratified patient population enrolled in the economic model (see Section B.3.2.1 for further information), a series of post hoc subgroup analyses for NAVIGATOR and SOURCE, were undertaken.

B.2.7.2.1 NAVIGATOR

Sum of all post hoc subgroups (3+ exacerbations OR mOCS)

This population aligns to the totality of the modelled populations. This includes the populations aligned to current NICE-approved biologics for benralizumab, mepolizumab, omalizumab, and dupilumab plus the residual patients with 3 or more exacerbations or mOCS who are not currently eligible for biologic treatment (see Table 97 in Section B.3.2.1 for more information). Table 48 to Table 51 present data specific for this subgroup from NAVIGATOR.

Table 48: Demographic characteristics: Sum of all post hoc subgroups (FAS)†

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Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Subjects who appeared in >1 of the post hoc subgroups described below were single counted in this subgroup.
‡ Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 49: AAER ratio over 52 weeks: Sum of all post hoc subgroups (negative binomial model; FAS)

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

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set.
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.

Table 50: CFB to Week 52 in pre-BD FEV_1: Sum of all post hoc subgroups (MMRM; FAS)

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[redacted]	[redacted]	[redacted]
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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; SE, standard error.
The model with unstructured covariance structure was: CFB in FEV_1 = treatment group + region + age + baseline FEV_1 + 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.

Table 51: CFB to Week 52 in ACQ-6: Sum of all post hoc subgroups (MMRM; FAS)

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

Anti-IL-5 eligible subgroup

This population 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) (see Table 97 in Section B.3.2.1 for more information).

Table 52 to Table 55 present data specific for this subgroup from NAVIGATOR.

Table 52: Demographic characteristics: Anti-IL-5 eligible subgroup (FAS)

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Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 53: AAER ratio over 52 weeks: Anti-IL-5 eligible subgroup (negative binomial model; FAS)

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[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.

Table 54: CFB to Week 52 in pre-BD FEV_1: Anti-IL-5 eligible subgroup (MMRM; FAS)

[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; IL, interleukin; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error.
The model with unstructured covariance structure was: CFB in FEV_1 = treatment group + region + age + baseline FEV_1 + 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.

Table 55: CFB to Week 52 in ACQ-6: Anti-IL-5 eligible subgroup (MMRM; FAS)

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

Dupilumab eligible subgroup

This population 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 (see Table 97 in Section B.3.2.1 for more information). Table 56 to Table 59 present data specific for this subgroup from NAVIGATOR.

Table 56: Demographic characteristics: Dupilumab eligible subgroup (FAS)

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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 57: AAER ratio over 52 weeks: Dupilumab eligible subgroup (negative binomial model; FAS)

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; FAS, full analysis set.
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.

Table 58: CFB to Week 52 in pre-BD FEV_1: Dupilumab eligible subgroup (MMRM; FAS)

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; SE, standard error.
The model with unstructured covariance structure was: CFB in FEV_1 = treatment group + region + age + baseline FEV_1 + 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.

Table 59: CFB to Week 52 in ACQ-6: Dupilumab eligible subgroup (MMRM; FAS)

[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.
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.

Omalizumab eligible subgroup

This population 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) (see Table 97 in Section B.3.2.1 for more information). Table 60 to Table 63 present data specific for this subgroup from NAVIGATOR.

Table 60: Demographic characteristics: Omalizumab eligible subgroup (FAS)

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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 61: AAER ratio over 52 weeks: Omalizumab eligible subgroup (negative binomial model; FAS)

	[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.
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.

Table 62: CFB to Week 52 in pre-BD FEV_1: Omalizumab eligible subgroup (MMRM; FAS)

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

Abbreviations: BD, bronchodilator; CFB, change from baseline; FEV_1, 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 FEV_1 = treatment group + region + age + baseline FEV_1 + 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.

Table 63: CFB to Week 52 in ACQ-6: Omalizumab eligible subgroup (MMRM; FAS)

[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.
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.

Non-bio eligible (3+ exacerbations OR mOCS)

This population aligns to the residual 3 or more exacerbation or mOCS patient population who are not currently eligible for biologic treatment (see Table 97 in Section B.3.2.1 for more information). Table 64 to Table 67 present data specific for this subgroup from NAVIGATOR.

Table 64: Demographic characteristics: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (FAS)

	[redacted]	[redacted]	[redacted]
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Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 65: AAER ratio over 52 weeks: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (negative binomial model; FAS)

	[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; mOCS, maintenance oral corticosteroid treatment.
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.

Table 66: CFB to Week 52 in pre-BD FEV_1: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (MMRM; FAS)

	[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.
The model with unstructured covariance structure was: CFB in FEV_1 = treatment group + region + age + baseline FEV_1 + 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.

Table 67: CFB to Week 52 in ACQ-6: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (MMRM; FAS)

	[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.

B.2.7.2.2 SOURCE

Sum of all post hoc subgroups (3+ exacerbations OR mOCS)

This population aligns to the totality of the modelled populations. This includes the populations aligned to current NICE-approved biologics for benralizumab, mepolizumab, omalizumab, and dupilumab plus the residual patients with 3 or more exacerbations who are not currently eligible for biologic treatment (see Table 97 in Section B.3.2.1 for more information). Table 68 to Table 71 present data specific for this subgroup from SOURCE.

Table 68: Demographic characteristics: Sum of all post hoc subgroups (FAS)[†]

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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA,

leukotriene receptor antagonist; max, maximum; min, minimum; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SD, standard deviation.
† Subjects who appeared in >1 of the post hoc subgroups described below were single counted in this subgroup.
‡ Calculated as (date of randomisation – date of asthma diagnosis/date asthma symptoms started +1) / 365.25.

Table 69: AAER ratio over 48 weeks: Sum of all post hoc subgroups (negative binomial model; FAS)

	[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.
A rate ratio less than 1 favours Tezepelumab. A negative binomial regression analysis with treatment, region, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable. Annual exacerbation rates and absolute differences displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences are estimated via the delta method.

Table 70: CFB to Week 48 in pre-BD FEV_1: Sum of all post hoc subgroups (MMRM; FAS)

	[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.

Table 71: CFB to Week 40 in ACQ-6: Sum of all post hoc subgroups (MMRM; FAS)

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

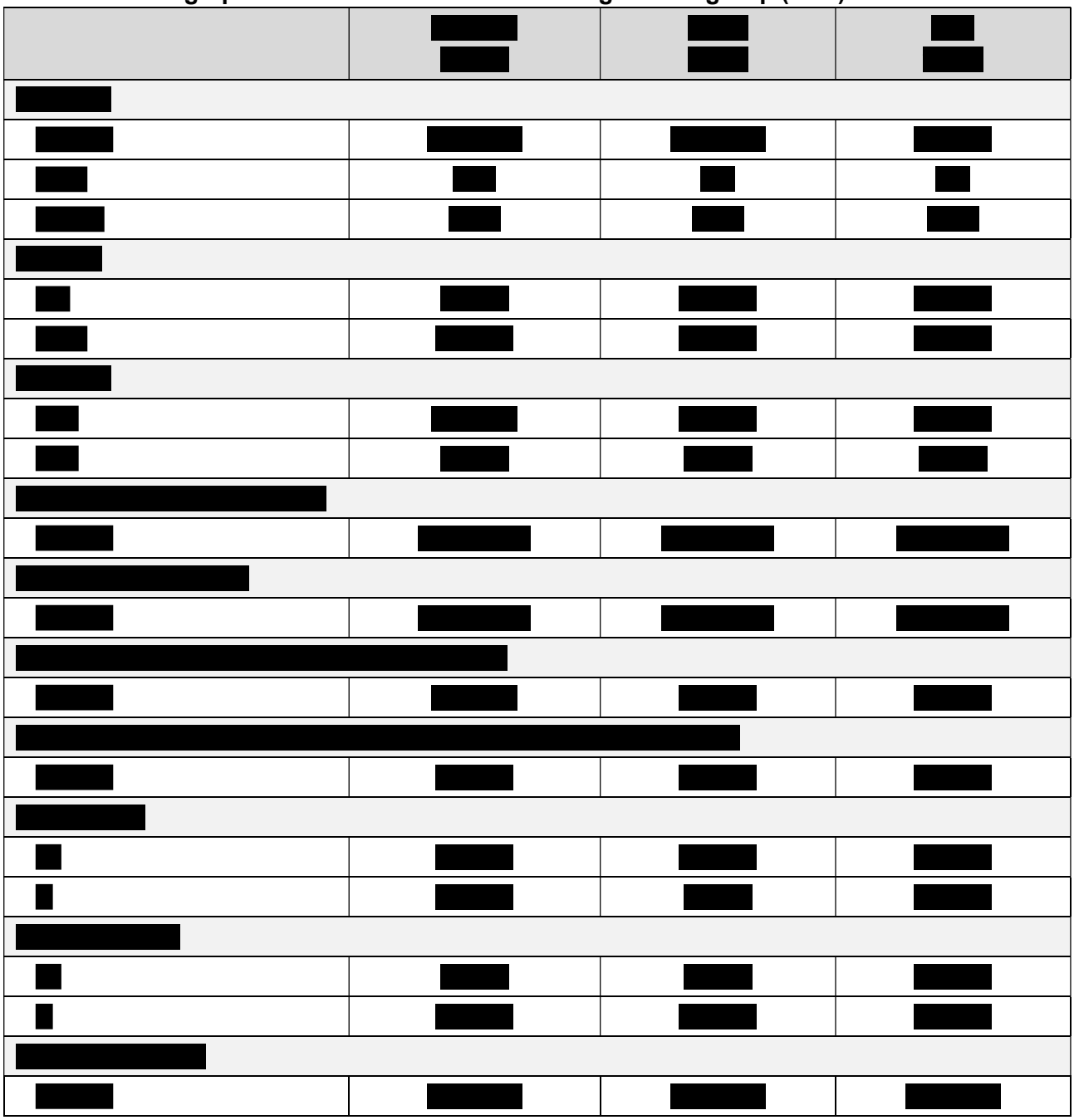
Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures.
Baseline is defined as the last non-missing measurement recorded on or prior to randomisation.

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.

Anti-IL-5 eligible subgroup

This population 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) (see Table 97 in Section B.3.2.1 for more information). Table 72 to Table 75 present data specific for this subgroup from SOURCE.

Table 72: Demographic characteristics: Anti-IL-5 eligible subgroup (FAS)



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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IL, interleukin; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis +1) / 365.25.

Table 73: AAER ratio over 48 weeks: Anti-IL-5 eligible subgroup (negative binomial model; FAS)

	[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 less than 1 favours Tezepelumab. A negative binomial regression analysis with treatment, region, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable. Annual exacerbation rates and absolute differences displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences are estimated via the delta method.

Table 74: CFB to Week 48 in pre-BD FEV1: Anti-IL-5 eligible subgroup (MMRM; FAS)

[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; IL, interleukin; LS, least squares; MMRM, mixed-effects model for repeated measures; 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.

Table 75: CFB to Week 48 in ACQ-6: Anti-IL-5 eligible subgroup (MMRM; FAS)

[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; IL, interleukin; 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.

Omalizumab eligible subgroup

This population 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) (see Table 97 in Section B.3.2.1 for more information). Table 76 to Table 79 present data specific for this subgroup from SOURCE.

Table 76: Demographic characteristics: Omalizumab eligible subgroup (FAS)

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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation – date of asthma diagnosis +1) / 365.25.

Table 77: AAER ratio over 48 weeks: Omalizumab eligible subgroup (negative binomial model; FAS)

[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.
A rate ratio less than 1 favours Tezepelumab. A negative binomial regression analysis with treatment, region, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable. Annual exacerbation rates and absolute differences displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences are estimated via the delta method.

Table 78: CFB to Week 48 in pre-BD FEV_1: Omalizumab eligible subgroup (MMRM; FAS)

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

Abbreviations: BD, bronchodilator; CFB, change from baseline; FEV_1, forced expiratory volume in the first second; LS, least squares; MMRM, mixed-effects model for repeated measures; 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.

Table 79: CFB to Week 48 in ACQ-6: Omalizumab eligible subgroup (MMRM; FAS)

[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.

Non-bio eligible (3+ exacerbations OR mOCS)

This population aligns to the residual 3 or more exacerbation or mOCS patient population who are not currently eligible for biologic treatment (see Table 97 in Section B.3.2.1 for more information). Table 80 to Table 83 present data specific for this subgroup from SOURCE.

Table 80: Demographic characteristics: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (FAS)

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

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardised) for 12 years and older; ASD, Asthma Symptom Diary; ER, emergency room; FAS, full analysis set; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; min, minimum; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SD, standard deviation.
† Calculated as (date of randomisation - date of asthma diagnosis +1)/365.25.

Table 81: AAER ratio over 48 weeks: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (negative binomial model; FAS)

[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; mOCS, maintenance oral corticosteroid treatment.
A rate ratio less than 1 favours Tezepelumab. A negative binomial regression analysis with treatment, region, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable. Annual exacerbation rates and absolute differences displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates. CIs for annual exacerbation rates and absolute differences are estimated via the delta method.

Table 82: CFB to Week 48 in pre-BD FEV_1: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (MMRM; FAS)

	[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.

Table 83: CFB to Week 48 in ACQ-6: Non-bio eligible (3+ exacerbations OR mOCS) subgroup (MMRM; FAS)

	[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.
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 Heterogeneous Toeplitz 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.

Dupilumab eligible subgroup

The dupilumab eligible population does not include patients on mOCS and therefore no subgroup data from SOURCE has been included.

B.2.8 Meta-analysis

A pooled analysis of PATHWAY and NAVIGATOR results was conducted the results of which were broadly consistent with those observed in the individual trials. Overall, the pooled analysis demonstrated that, in subjects with severe, uncontrolled asthma, tezepelumab substantially reduces asthma exacerbations, including those resulting in an ER visit or hospitalisation, when compared with placebo. This was observed in a broad population of patients with severe, uncontrolled asthma and across subgroups based on baseline blood eosinophil count, FeNO, perennial allergic status, and maintenance OCS

use. Greater improvements in FEV_1, AQLQ(S)+12, and ACQ-6 were also observed with tezepelumab treatment versus placebo.

Results of the pooled analysis are presented in Appendix D.

B.2.9 Indirect and mixed treatment comparisons

SUMMARY

- The highest ranked biologic in the primary analyses of each of the following outcomes considered in the network meta-analysis (NMA) were as follows:
  - Reduction in AAER: Tezepelumab
  - Reduction in AAER leading to hospitalisation: Tezepelumab
  - [redacted]
  - [redacted]
  - [redacted]
- 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), [redacted] 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)
  - Reduction in AAER (low blood EOS level (300 cells/μL)
  - Reduction in AAER (allergic asthma)
  - Reduction in AAERs leading to hospitalisation (primary analysis)
- [redacted]
- Overall, in each NMA that informed the model, 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

B.2.9.1 Methodology

No head-to-head trials have yet compared the efficacy of tezepelumab with that of other biologics approved for the treatment of severe uncontrolled asthma. In the absence of

direct evidence, an indirect treatment comparison (network meta-analyses) was undertaken, full details for which are provided in Appendix D. Note that an STC analysis was also performed, but since it does not inform the model, it is presented in Appendix D.

B.2.9.1.1 Outcomes of interest

The five outcomes assessed in the NMAs were: reduction in AAER (count), reduction in AAER leading to hospitalisations (count), change from baseline in ACQ score (continuous), change from baseline in pre-BD FEV_1 (continuous), and change from baseline in OCS dose by predefined mutually exclusive reduction categories (ordinal).

B.2.9.1.2 Study selection

The clinical efficacy and safety SLR described in B.2.2 identified a total of 39 RCTs for potential inclusion in NMAs. Three studies were excluded prior to the feasibility assessment because they did not report any of the main outcomes of interest. Therefore, 36 RCTs were considered for inclusion in each of the NMAs (Table 84).

Details of the feasibility assessment are provided in Appendix D.

Table 84: List of RCTs included in the feasibility assessment

Benralizumab	Dupilumab	Mepolizumab	Omalizumab	Reslizumab	Tezepelumab
SIROCCO (2016) CALIMA (2016) ZONDA (2017) ALIZE (2018) ANDHI (2020) SOLANA (2020)	Wenzel (2016) LIBERTY ASTHMA QUEST (2018) LIBERTY ASTHMA VENTURE (2018)	MENSA (2014) SIRIUS (2014) MUSCA (2017)	Ayres (2004) Holgate (2004) INNOVATE (2005) NCT00567476 (2007) Ohta (2009) Chanez (2010) EXALT (2011) Hanania (2011) Bardelas (2012) Hoshino (2012) QUALITX (2012) Busse (2013) NATAIR (2013) Pasha (2014) Li (2016) Mukherjee (2019)	Castro (2011) Castro (2015) Bjermer (2016) Corren (2016)	PATHWAY (2017) NAVIGATOR (2020) SOURCE (2020)

Abbreviations: RCT, randomised controlled trial.

B.2.9.1.3 Evidence networks

For each of the outcomes studied, evidence networks were developed to assess the feasibility of conducting NMAs between tezepelumab and the comparator biologics. Network diagrams for each of the five outcomes are presented in the following sections. Within these networks, each drug is represented by a node and randomised comparisons between drugs are depicted by links between nodes. The size of the node is reflective of the sample size and the width of the link is reflective of the number of studies connecting the treatment options. Notably, evidence networks were developed for the analysis to be performed at the drug level and were stratified by individual approved doses of the various treatment regimens to reduce risk of heterogeneity.

B.2.9.1.4 Statistical analysis

Bayesian NMAs were performed for each of the five outcomes. Standard ITC methodology based on NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 2 was followed (113). The chosen reference treatment for all analyses was placebo, given that most RCTs included in the ITC were placebo-controlled. Notably, five RCTs assessing omalizumab (Ayres [2004] (114), NCT0056746 [2007] (115), EXALT [2011] (116), Hoshino [2012] (117), and QUALITX [2012] (118)) were not placebo-controlled; Ayres (2004) (114) used BSC, EXALT (2011) (116) used OAT, and NCT0056746 [2007] (115), Hoshino [2012] (117), and QUALITX [2012] (118) used ICS and LABA as the comparators. However, BSC, OAT, and prescribed ICS and LABA were considered equivalent to placebo for networks that include these RCTs. This assumption was tested using sensitivity analyses that excluded omalizumab studies that were not placebo-controlled for all outcomes except OCS reduction (see Section B.2.9.3.4).

Both fixed effects and random effects models were considered for NMAs of each outcome. Vague or flat priors, such as $N(0, 100^2)$, were assigned for basic parameters. Model selection was based on model fit statistics (i.e. deviance information criterion [DIC], total residual deviance [TRD], and random effects standard deviation), total number of studies and studies per connection, and plausibility of results.

NMAs were performed using R statistical software (version 3.5.3) with R package ‘rjags’ (version 4-8) to interface with Just Another Gibbs Sampler (JAGS) software (version 4.3.0) for both model specification and Bayesian estimation.

Full details of the methodology for the indirect comparison/ mixed treatment comparison are provided in Appendix D.

B.2.9.2 Results

Pairwise comparisons from the NMA are presented as league tables in which the treatment with the most favourable estimate is positioned in the top left corner, with the second, third, etc. most favourable treatments shown in descending order to the right. Surface under the cumulative ranking curve (SUCRA) values were generated as an additional measure to reflect ranking and uncertainty. This measure, expressed as a percentage, shows the relative probability of an intervention being among the best options. SUCRA values range between 0 and 100; values nearer to 100 reflect a higher ranking (119).

Note that dupilumab 300 mg was included in the networks to power the analyses, but outcomes should not be deemed relevant since this dose is not recommended by NICE (only the 200 mg dose is recommended) (94).

Only those NMA results that inform the cost-effectiveness model described in Section B.3 are presented below. The remainder are presented in Appendix D as follows:

- Reduction in AAER – Section B.2.9.2.1
- Reduction in AAER leading to hospitalisations – Section B.2.9.2.2
- Change from baseline in OCS dose according to predefined reduction category – Section B.2.9.2.3
- Change from baseline in ACQ score – Appendix D
- Change from baseline in pre-BD FEV1 – Appendix D

B.2.9.2.1 Reduction in AAER

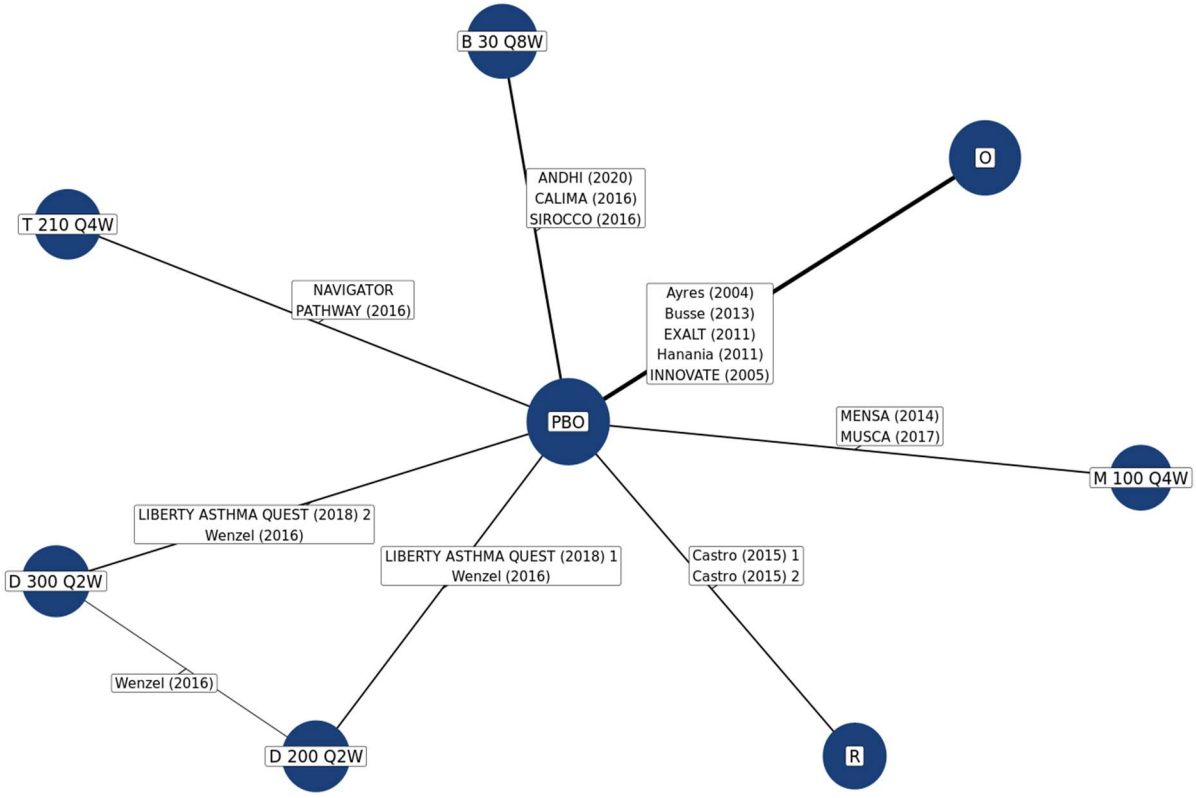
The evidence network for reduction in AAER is presented in Figure 27. The common comparator across all trials was placebo, with a single multi-dose study creating one closed loop. The network included 16 studies consisting of 10,092 patients (see Appendix D).

Figure 28 shows a league table of findings from the random effects (vague priors) NMA. Tezepelumab 210 mg Q4W was the most favourable treatment with a rate ratio of 0.37 (95% CrI 0.23, 0.57) and was numerically better than dupilumab, mepolizumab, reslizumab, and benralizumab and omalizumab. No other differences between biologics

were observed. (Please see AAER subgroup analyses below, however, where some statistically significant results in favour of tezepelumab were observed). All treatments were statistically significantly better than placebo. The DIC was 319.09 and the total residual deviance (TRD) was 34.88 (35 data points). Based on the number of studies and adequate model fit statistics, the random effects model was considered the best fit.

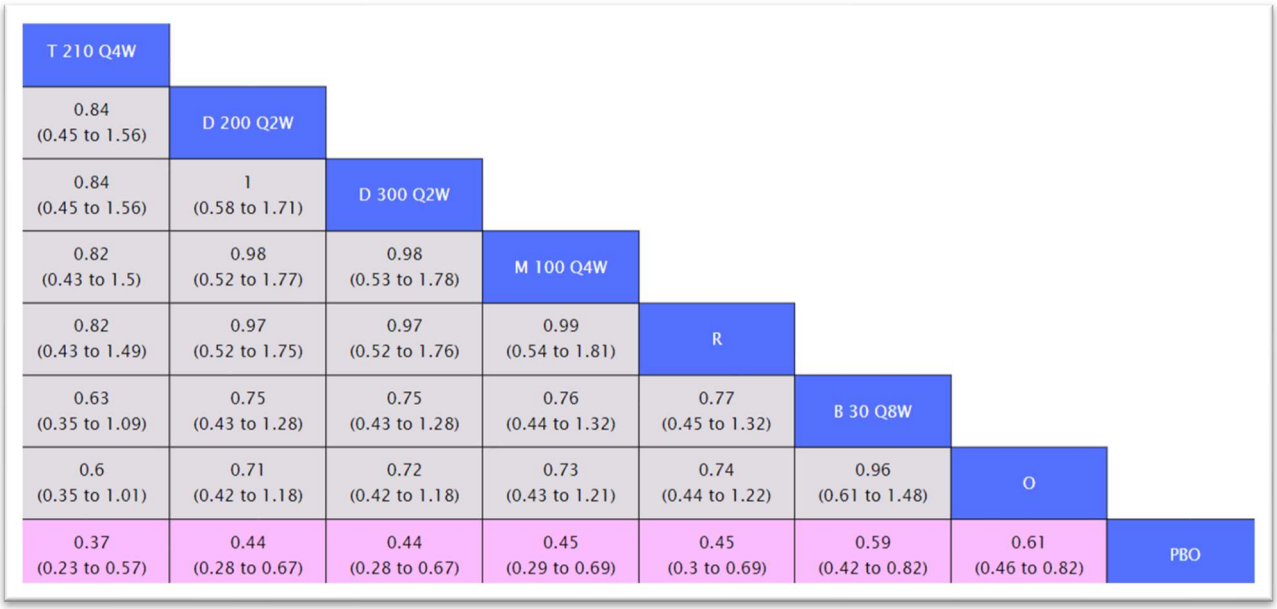
Table 85 shows the SUCRA values and probability of being best for the reduction in AAER. In line with the league table, tezepelumab 210 mg Q4W was associated with the highest SUCRA value of 84%.

Figure 27: Evidence network for reduction in AAER (ITT)



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; BSC, best supportive care; D, dupilumab; ITT, intent-to-treat; M, mepolizumab; NICE, National Institute for Health and Care Excellence; O, omalizumab; OAT, optimised asthma therapy; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; R, reslizumab; T, tezepelumab.
EXALT (2011) and Ayres (2004) studies were versus OAT and BSC, respectively, which were assumed to be equivalent to PBO.
Note: D 300 Q2W is not a NICE-recommended dose.

Figure 28: Pairwise comparisons from the random effects (vague priors) NMA for reduction in AAER (ITT)



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.

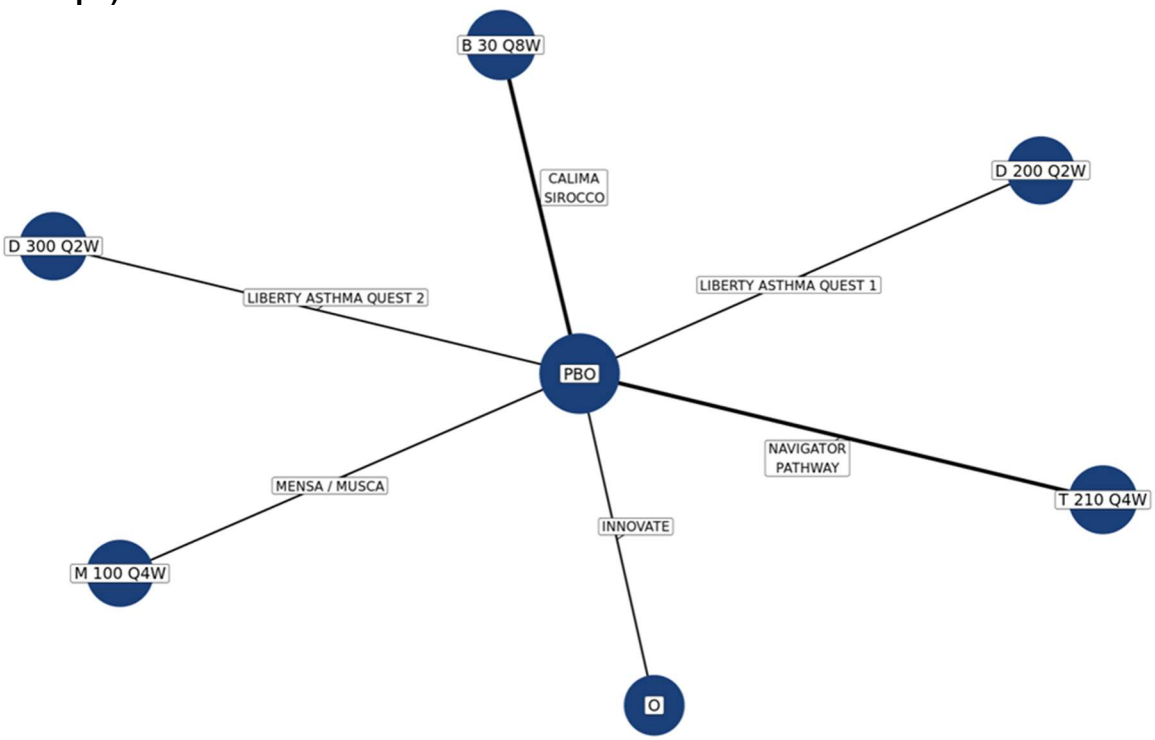
Table 85: Summary of SUCRA values from random effects (vague priors) NMA for reduction in AAER

Treatment	SUCRA (%)	Probability best (%)
Tezepelumab	84	48
Dupilumab 200 mg	66	14
Dupilumab 300 mg†	66	14
Mepolizumab	64	12
Reslizumab	63	11
Benralizumab	31	0
Omalizumab	26	0
Placebo	0	0

Abbreviations: AAER, annualised asthma exacerbation rate; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking.
† Not a NICE-recommended dose.

B.2.9.2.1.1 High blood EOS level (≥150 cells/µL)

Figure 29: Evidence network for reduction in AAER: High blood EOS level subgroup (≥150 cells/µL)



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.

Figure 30: Pairwise comparisons from the fixed effects NMA for reduction in AAER: High blood EOS level subgroup (≥150 cells/µL)

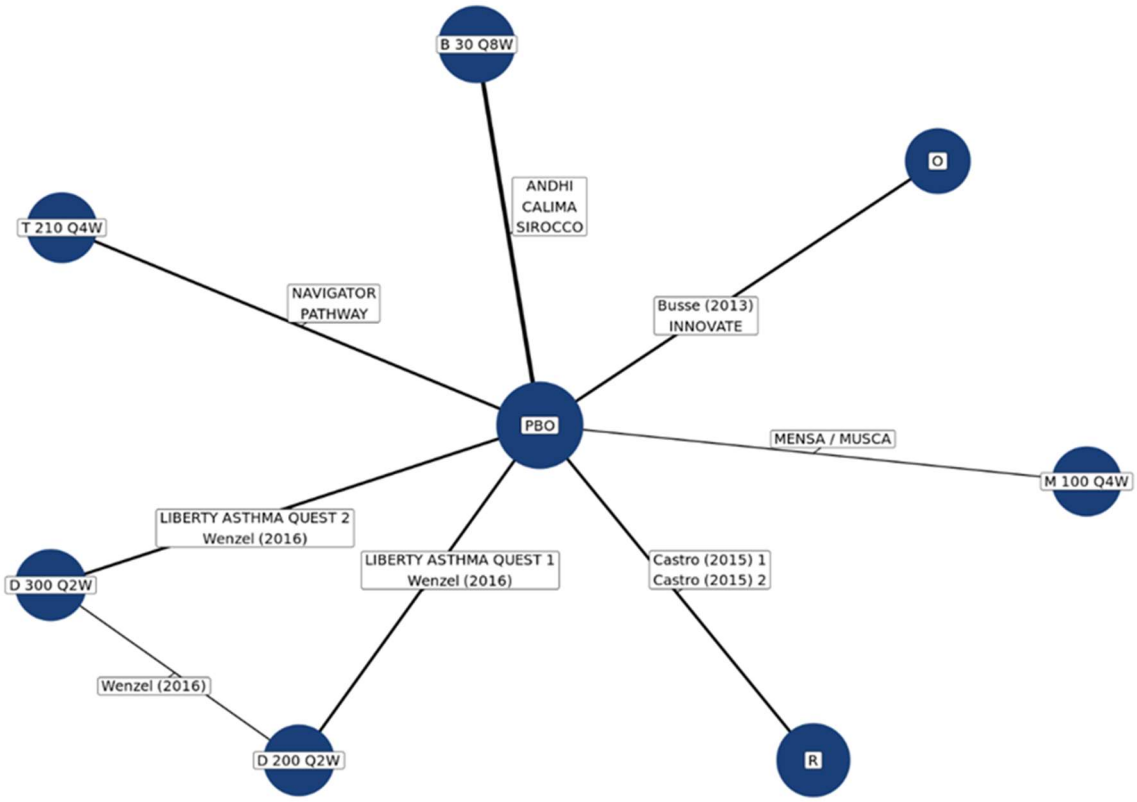
T 210 Q4W						
0.94 (0.68 to 1.3)	M 100 Q4W					
0.91 (0.58 to 1.44)	0.97 (0.61 to 1.57)	D 300 Q2W				
0.84 (0.54 to 1.33)	0.9 (0.56 to 1.45)	0.93 (0.52 to 1.62)	D 200 Q2W			
0.63 (0.43 to 0.94)	0.67 (0.44 to 1.04)	0.69 (0.41 to 1.17)	0.75 (0.44 to 1.27)	O		
0.63 (0.49 to 0.82)	0.68 (0.5 to 0.92)	0.69 (0.45 to 1.08)	0.75 (0.48 to 1.16)	1 (0.69 to 1.47)	B 30 Q8W	
0.38 (0.32 to 0.47)	0.41 (0.32 to 0.53)	0.42 (0.28 to 0.63)	0.46 (0.3 to 0.68)	0.61 (0.43 to 0.86)	0.61 (0.51 to 0.72)	PBO

Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; CrI, credible interval; D, dupilumab; EOS, eosinophil; 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.

B.2.9.2.1.2 High blood EOS level (≥300 cells/µL)

Figure 31: Evidence network for reduction in AAER: High blood EOS level subgroup (≥300 cells/µL)



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.

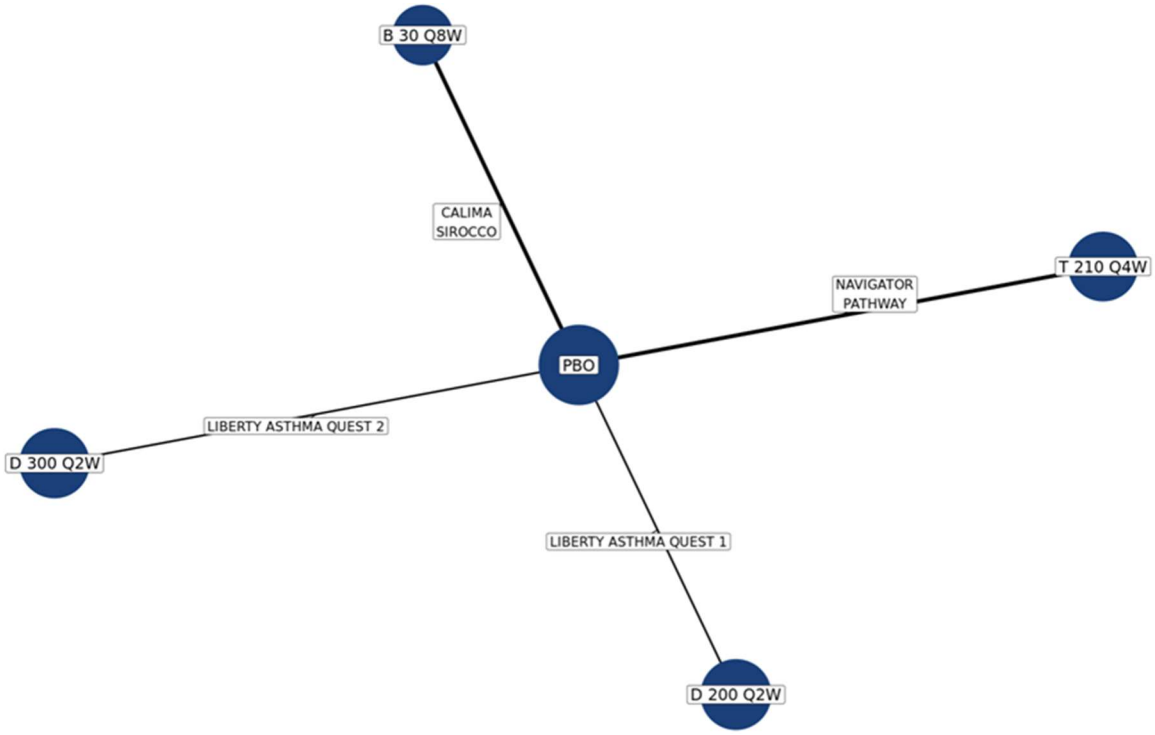
Figure 32: Pairwise comparisons from the fixed effects NMA for reduction in AAER: High blood EOS level subgroup (≥300 cells/µL)

D 300 Q2W							
0.93 (0.44 to 1.86)	T 210 Q4W						
0.89 (0.44 to 1.7)	0.95 (0.47 to 1.92)	D 200 Q2W					
0.84 (0.37 to 1.77)	0.89 (0.42 to 1.95)	0.94 (0.43 to 2.09)	M 100 Q4W				
0.66 (0.32 to 1.27)	0.7 (0.37 to 1.37)	0.74 (0.38 to 1.46)	0.79 (0.38 to 1.63)	R			
0.56 (0.26 to 1.19)	0.6 (0.29 to 1.3)	0.64 (0.3 to 1.37)	0.68 (0.31 to 1.55)	0.86 (0.43 to 1.75)	O		
0.57 (0.3 to 1.04)	0.6 (0.34 to 1.13)	0.64 (0.35 to 1.19)	0.68 (0.34 to 1.37)	0.86 (0.49 to 1.51)	1.01 (0.52 to 1.91)	B 30 Q8W	
0.3 (0.17 to 0.5)	0.32 (0.2 to 0.53)	0.34 (0.2 to 0.56)	0.36 (0.2 to 0.65)	0.46 (0.3 to 0.7)	0.53 (0.3 to 0.93)	0.53 (0.37 to 0.75)	PBO

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.

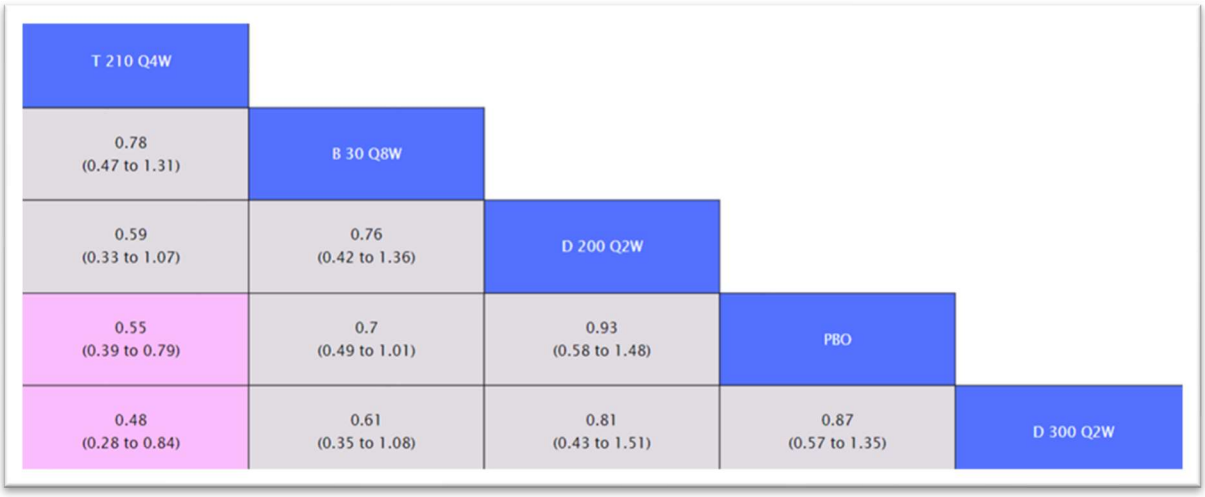
B.2.9.2.1.3 Low blood EOS level (<150 cells/µL)

Figure 33: Evidence network for reduction in AAER: Low blood EOS level subgroup (<150 cells/µL)



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; D, dupilumab; EOS, eosinophil; NICE, National Institute for Health and Care Excellence; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

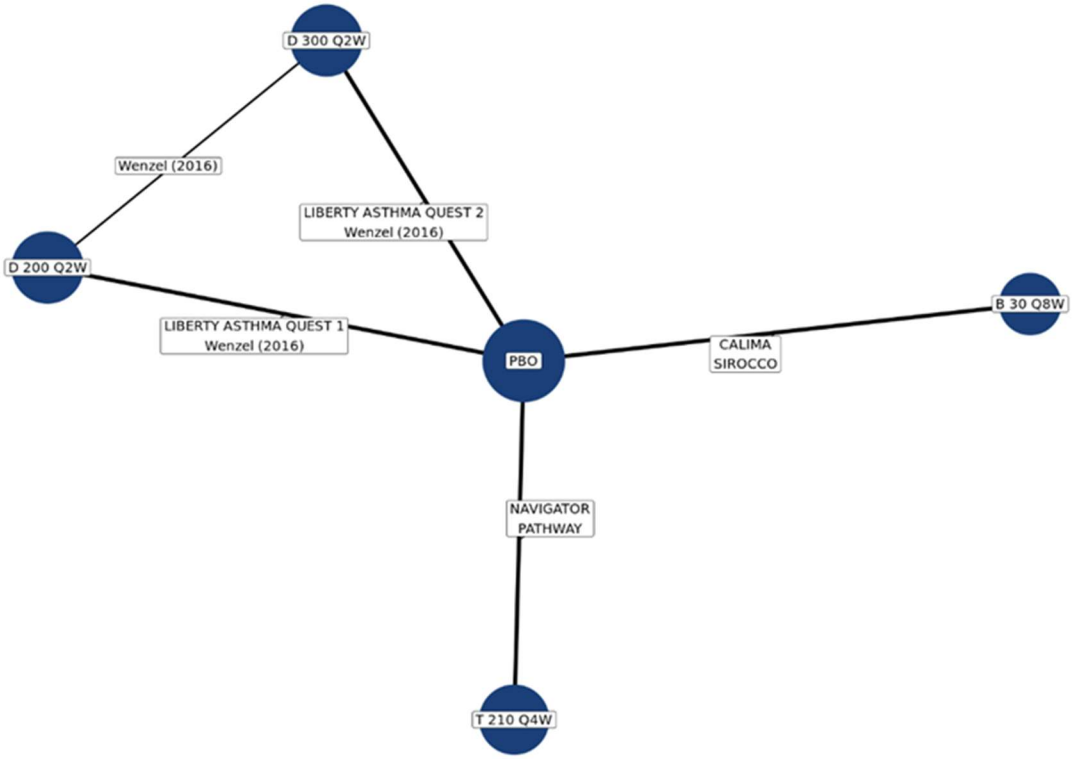
Figure 34: Pairwise comparisons from the fixed effects NMA for reduction in AAER: Low blood EOS level subgroup (<150 cells/μL)



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.

B.2.9.2.1.4 Low blood EOS level (<300 cells/µL)

Figure 35: Evidence network for reduction in AAER: Low blood EOS level subgroup (<300 cells/µL)



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; D, dupilumab; EOS, eosinophil; NICE, National Institute for Health and Care Excellence; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

Figure 36: Pairwise comparisons from the fixed effects NMA for reduction in AAER: Low blood EOS level subgroup (<300 cells/µL)

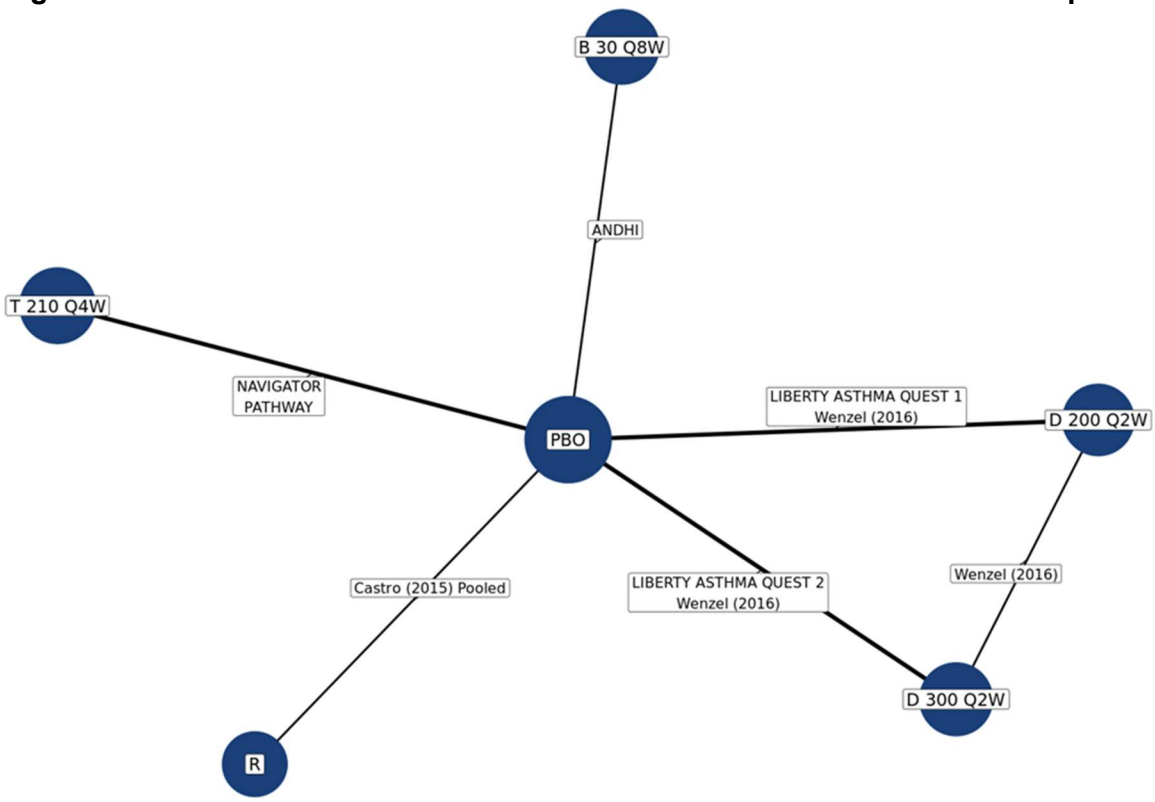
T 210 Q4W				
0.69 (0.12 to 3.32)	D 200 Q2W			
0.61 (0.1 to 2.83)	0.89 (0.22 to 3.54)	D 300 Q2W		
0.59 (0.1 to 2.62)	0.86 (0.15 to 4.25)	0.97 (0.18 to 4.92)	B 30 Q8W	
0.41 (0.11 to 1.18)	0.61 (0.18 to 1.84)	0.68 (0.2 to 2.12)	0.71 (0.22 to 2.27)	PBO

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.

B.2.9.2.1.5 ≥3 exacerbations in the prior 12 months

Figure 37: Evidence network for reduction in AAER: ≥3 exacerbations in the prior 12 months



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; D, dupilumab; NICE, National Institute for Health and Care Excellence; 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.

Figure 38: Pairwise comparisons from the fixed effects NMA for reduction in AAER: ≥3 exacerbations in the prior 12 months

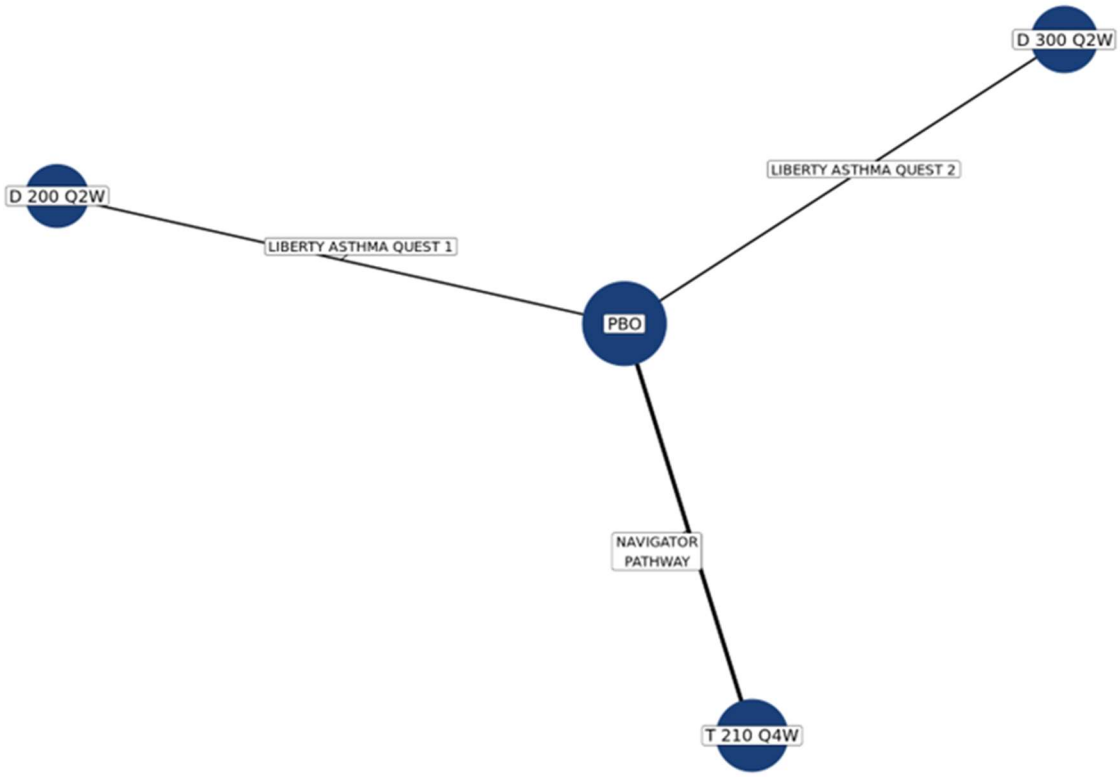
[redacted]

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; 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.

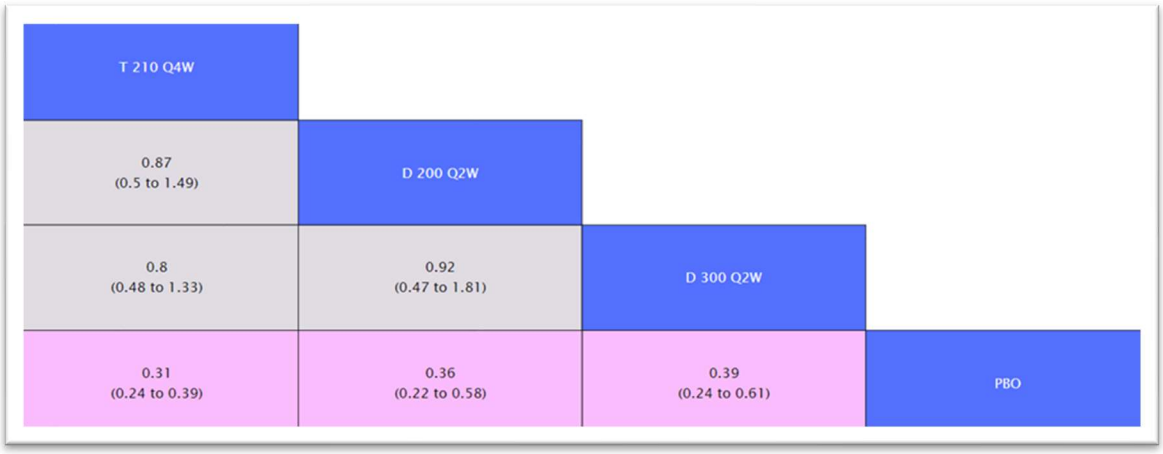
B.2.9.2.1.6 High FeNO level (≥25 ppb)

Figure 39: Evidence network for reduction in AAER: High FeNO level (≥25 ppb)



Abbreviations: AAER, annualised asthma exacerbation rate; D, dupilumab; FeNO, fractional exhaled nitric oxide; NICE, National Institute for Health and Care Excellence; PBO, placebo; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

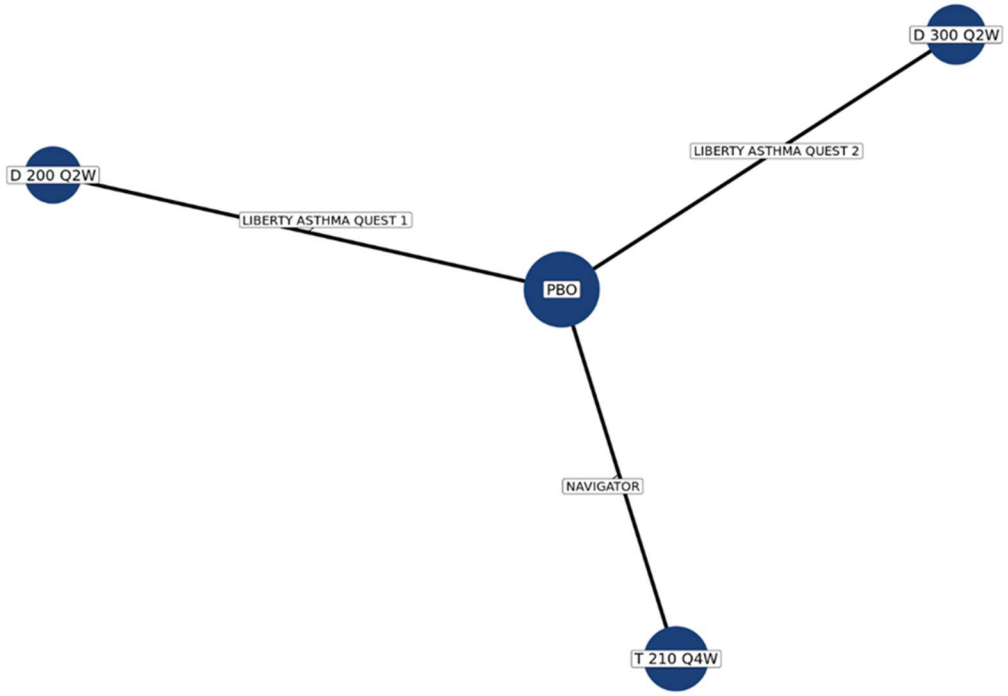
Figure 40: Pairwise comparisons from the fixed effects NMA for reduction in AAER: High FeNO level (≥25 ppb)



Abbreviations: AAER, annualised asthma exacerbation rate; CrI, credible interval; D, dupilumab; FeNO, fractional exhaled nitric oxide; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBO, placebo; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 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.

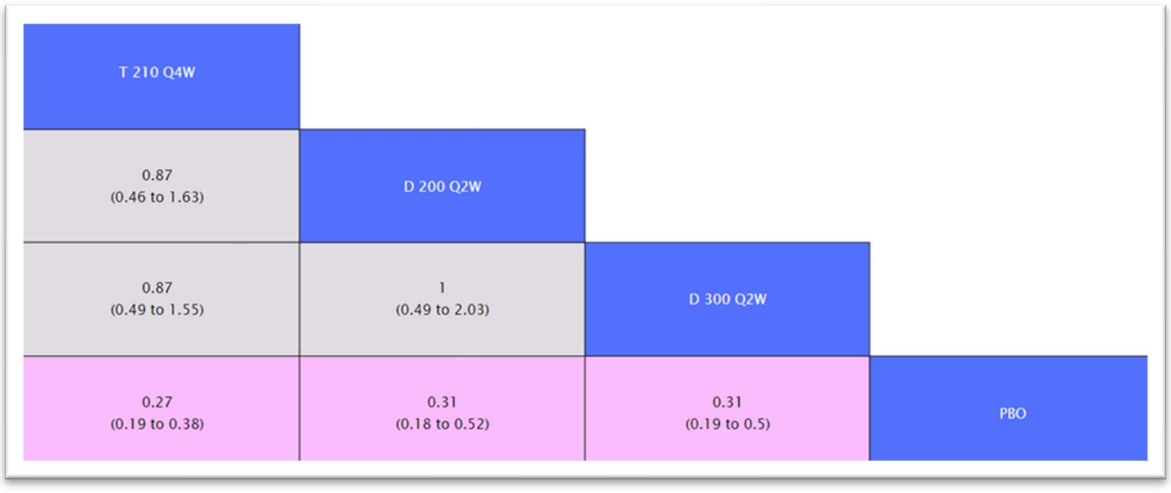
B.2.9.2.1.7 High FeNO level (≥50 ppb)

Figure 41: Evidence network for reduction in AAER: High FeNO level (≥50 ppb)



Abbreviations: AAER, annualised asthma exacerbation rate; D, dupilumab; FeNO, fractional exhaled nitric oxide; NICE, National Institute for Health and Care Excellence; PBO, placebo; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

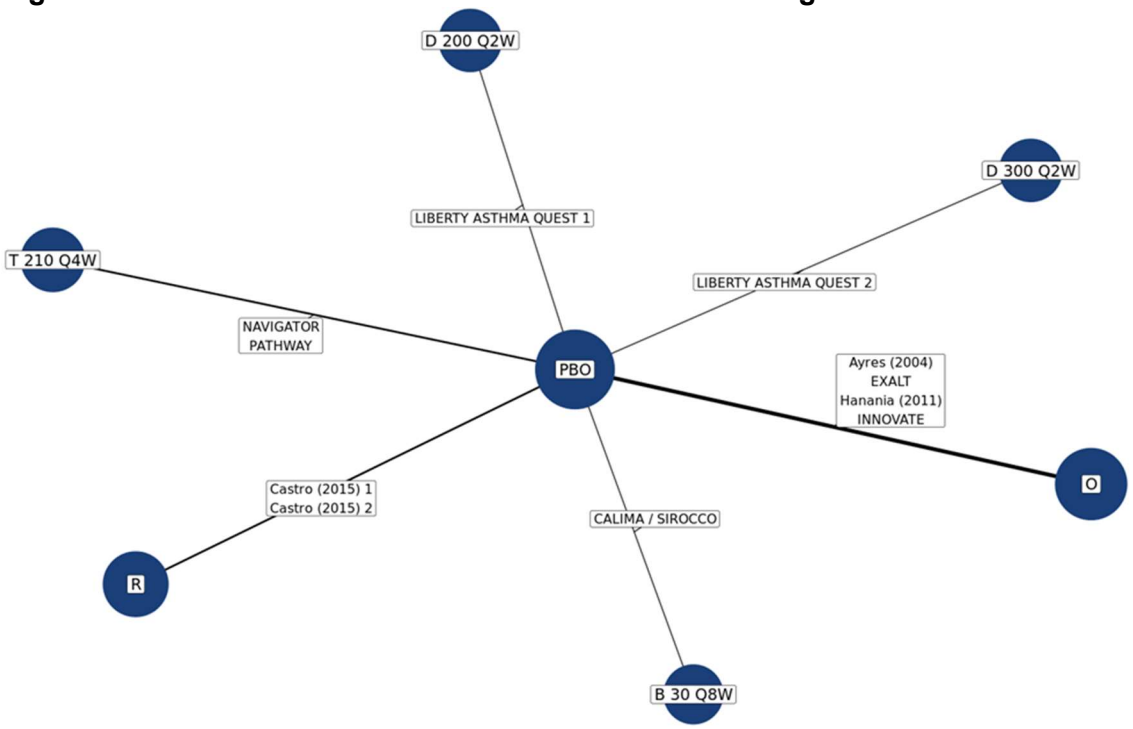
Figure 42: Pairwise comparisons from the fixed effects NMA for reduction in AAER: High FeNO level (≥50 ppb)



Abbreviations: AAER, annualised asthma exacerbation rate; CrI, credible interval; D, dupilumab; FeNO, fractional exhaled nitric oxide; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBO, placebo; ppb, parts per billion; Q2W, once every 2 weeks; Q4W, once every 4 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.

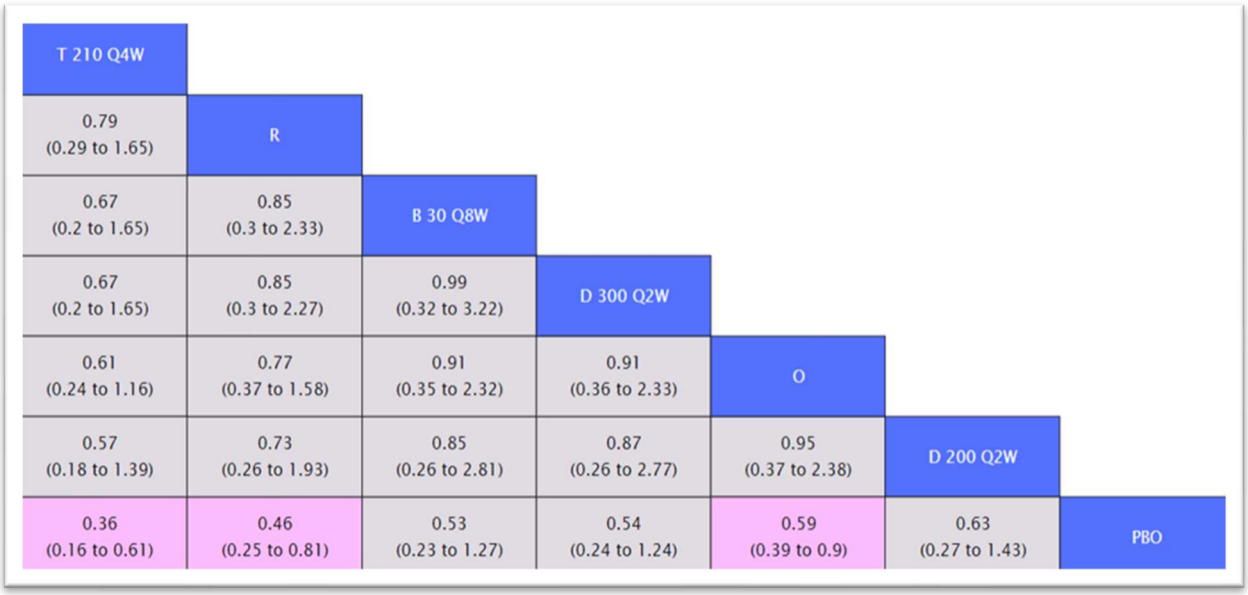
B.2.9.2.1.8 Allergic asthma

Figure 43: Evidence network for reduction in AAER: Allergic asthma



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; D, dupilumab; ITT, intent-to-treat; 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.

Figure 44: Pairwise comparisons from the fixed effects NMA for reduction in AAER: Allergic asthma



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.

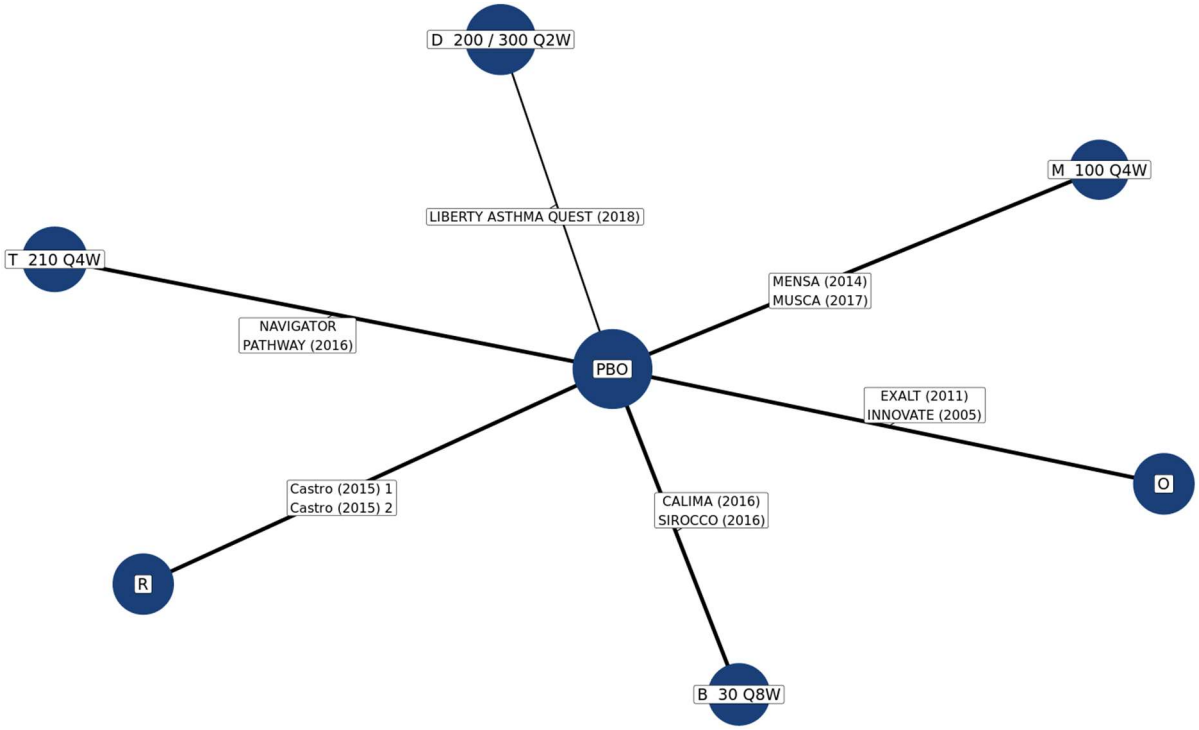
B.2.9.2.2 Reduction in AAER leading to hospitalisations

The evidence network for reduction in AAER leading to hospitalisations is presented in Figure 45. The common comparator across all trials was placebo. The network included 11 studies consisting of 6,965 patients. Unlike AAER, only pooled data were available for the two dosages (200 mg and 300 mg Q2W) of dupilumab from LIBERTY ASTHMA QUEST (2018). All trials except for one, EXALT (2011), reported the rate of exacerbations resulting in hospitalisation or emergency room/department visit. EXALT (2011) reported the rate of exacerbations resulting in hospitalisation.

Figure 46 shows a league table of findings from the random effects (vague priors) NMA. Tezepelumab 210 mg Q4W was positioned as the most favourable treatment with a rate ratio of 0.19 (95% CrI: 0.07, 0.47) and was numerically better than all other biologic comparators. Only tezepelumab and mepolizumab were statistically significantly better than placebo. The DIC was 151.89 and the TRD was 22.26 (22 data points). Based on the number of studies included and the adequate model fit statistics, the random effects model was considered the best fit.

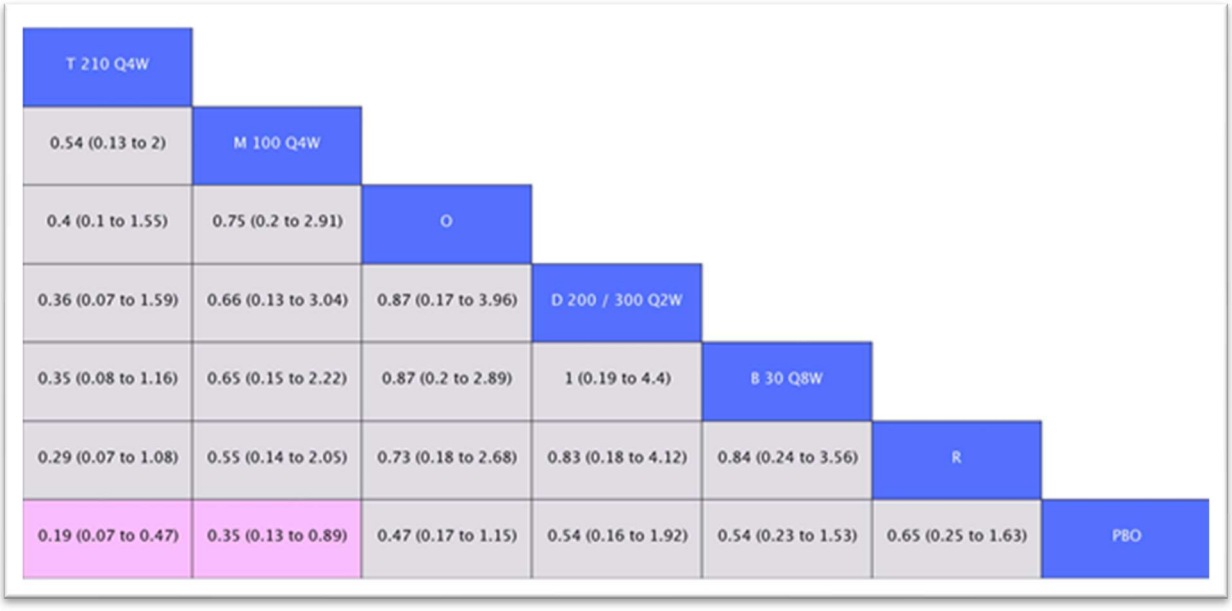
Table 86 shows the SUCRA values and probability of being best for the reduction in AAER leading to hospitalisations. In line with the league table, tezepelumab 210 mg Q4W was associated with the highest SUCRA value of 95%.

Figure 45: Evidence network for reduction in AAER leading to hospitalisations (ITT)



Abbreviations: AAER, annualised asthma exacerbation rate; B, benralizumab; BSC, best standard care; D, dupilumab; ITT, intent-to-treat; M, mepolizumab; NICE, National Institute for Health and Care Excellence; O, omalizumab; OAT, optimised asthma therapy; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; R, reslizumab; T, tezepelumab. EXALT (2011) compared omalizumab with OAT, which was assumed to be equivalent to PBO.
Note: D 300 Q2W is not a NICE-recommended dose.

Figure 46: Pairwise comparisons from random effects (vague priors) NMA for reduction AAER leading to hospitalisations (ITT)



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.

Table 86: Summary of SUCRA values from random effects (vague priors) NMA for reduction in AAER leading to hospitalisations

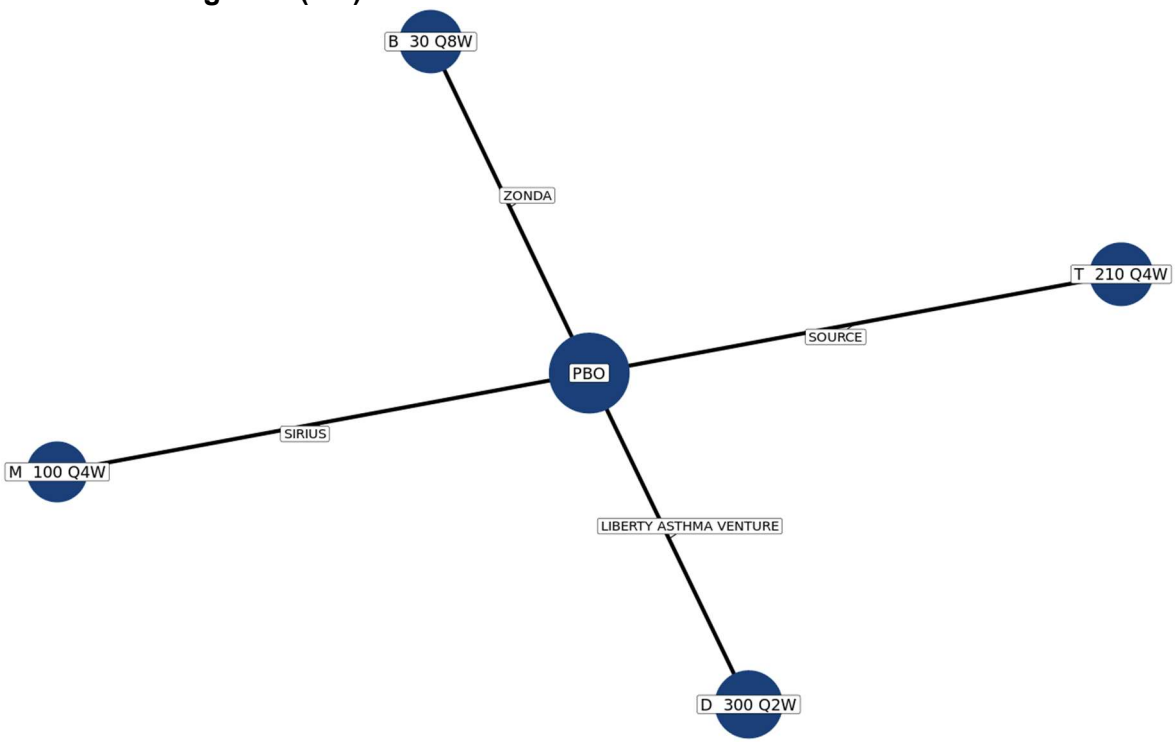
Treatment	SUCRA (%)	Probability best (%)
Tezepelumab	95	80
Dupilumab 200/300 mg †	45	4
Mepolizumab	71	10
Reslizumab	34	1
Omalizumab	54	4
Benralizumab	45	2
Placebo	6	0

Abbreviations: AAER, annualised asthma exacerbation rate; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking.
† Dupilumab 300 mg is not a NICE-recommended dose.

B.2.9.2.3 Change from baseline in OCS dose according to predefined reduction category

The evidence network for change from baseline OCS dose according to predefined reduction categories is shown in Figure 47. The common comparator across all trials was placebo. The network comprised four studies consisting of 643 patients.

Figure 47: Evidence network for change from baseline in OCS dose according to predefined reduction categories (ITT)



Abbreviations: B, benralizumab; D, dupilumab; ITT, intent-to-treat; M, mepolizumab; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

B.2.9.2.3.1 OCS dose reduction of ≥50, ≥75, or ≥90%

A league table summarising the findings from the fixed effects NMAs for change from baseline in the OCS dose by ≥50, ≥75, or ≥90% is presented in Figure 48.

[redacted]. The DIC was [redacted] and the TRD was [redacted] (32 data points). Based on the number of single study connections in the network and the model fit statistics, the fixed effects model was considered the best fit.

Note that SOURCE was the only trial to inform the network for tezepelumab for this endpoint (OCS dose reduction), and for the reasons described in Section B.2.13.2.1, SOURCE did not demonstrate a statistically significant difference between tezepelumab and placebo in categorised percent reduction in daily OCS dose.

Figure 48: Pairwise comparisons from the fixed effects NMA for change from baseline in OCS dose by ≥50%, ≥75% or ≥90% (ITT)

Abbreviations: 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; OCS, oral corticosteroid; 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.

Table 87 shows SUCRA values and probability of being best.

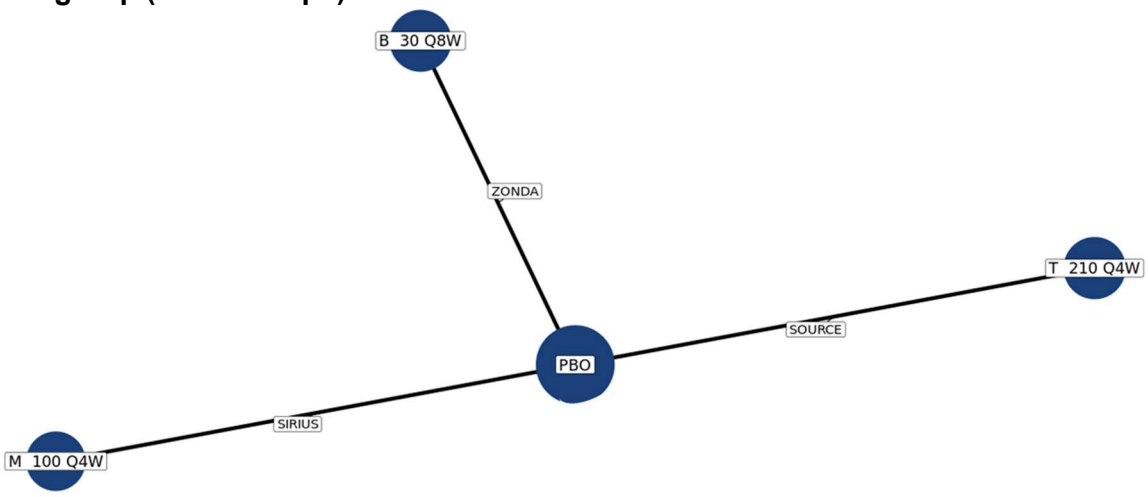
Table 87: Summary of SUCRA value from fixed effects NMA for change from baseline in OCS dose by ≥50, ≥75, or ≥90%

Treatment	SUCRA	Probability best

Abbreviations: NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OCS, oral corticosteroid; SUCRA, surface under the cumulative ranking.
† Dupilumab 300 mg is not a NICE-recommended dose.

High blood EOS level (≥150 cells/µL)

Figure 49: Evidence network for change from baseline in OCS dose: High blood EOS level subgroup (≥150 cells/µL)



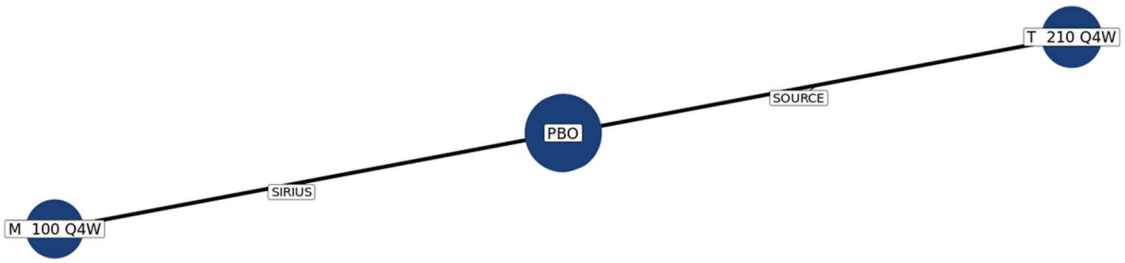
Abbreviations: B, benralizumab; D, dupilumab; EOS, eosinophil; M, mepolizumab; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; T, tezepelumab.

Figure 50: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose: High blood EOS level subgroup (≥150 cells/µL)

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.

High blood EOS level (≥300 cells/µL)

Figure 51: Evidence network for change from baseline in OCS dose: High blood EOS level subgroup (≥300 cells/µL)



Abbreviations: D, dupilumab; EOS, eosinophil; M, mepolizumab; OCS, oral corticosteroid; PBO, placebo; Q4W, once every 4 weeks; T, tezepelumab.

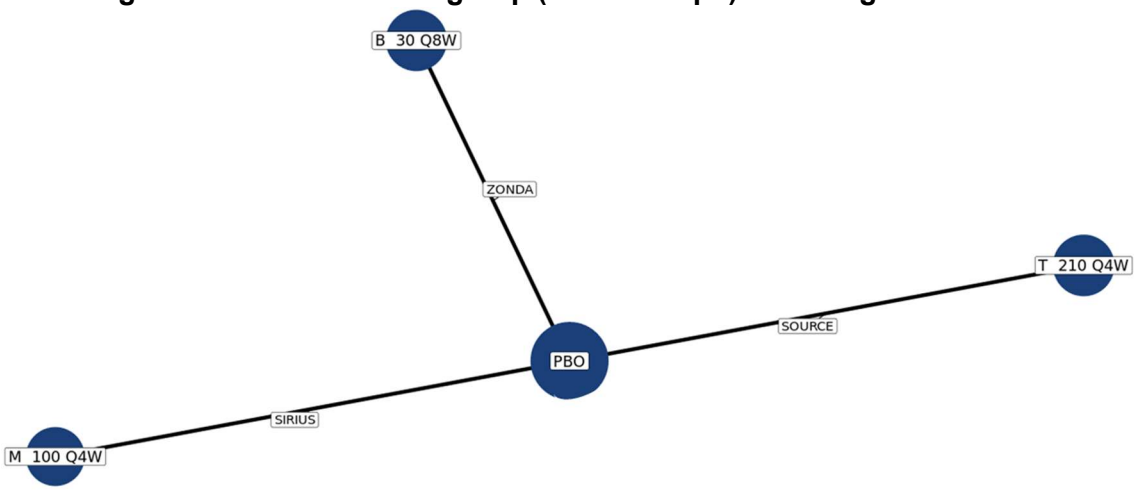
Figure 52: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose: High blood EOS level subgroup (≥300 cells/µL)

[redacted]

Abbreviations: CrI, credible interval; EOS, eosinophil; M, mepolizumab; NMA, network meta-analysis; OCS, oral corticosteroid; PBO, placebo; Q4W, once every 4 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.

High blood EOS level (≥300 cells/µL) including ZONDA

Figure 53: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose: High blood EOS level subgroup (≥300 cells/µL) including ZONDA



Abbreviations: B, benralizumab; EOS, eosinophil; M, mepolizumab; OCS, oral corticosteroid; PBO, placebo; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.

Figure 54: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose: High blood EOS level subgroup (≥300 cells/µL) including ZONDA

[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.

B.2.9.2.3.2 OCS dose reduction of ≥50%

A league table summarising the findings from the fixed effects NMA for change from baseline in OCS dose by ≥50% is presented in Figure 55.

[redacted]

. The rate ratio

for tezepelumab 210 mg Q4W was [redacted]. The DIC was [redacted] and the TRD was [redacted] (8 data points). Based on the number of single study connections in the network and the model fit statistics, the fixed effects model was considered the best fit.

Figure 55: Pairwise comparisons from the fixed effects NMA for change from baseline in OCS dose by ≥50% (ITT)

Abbreviations: 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; OCS, oral corticosteroid; 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.

Table 88 shows SUCRA values and probability of being best. In line with the league table, dupilumab 300 mg Q2W was associated with the highest SUCRA value of [redacted].

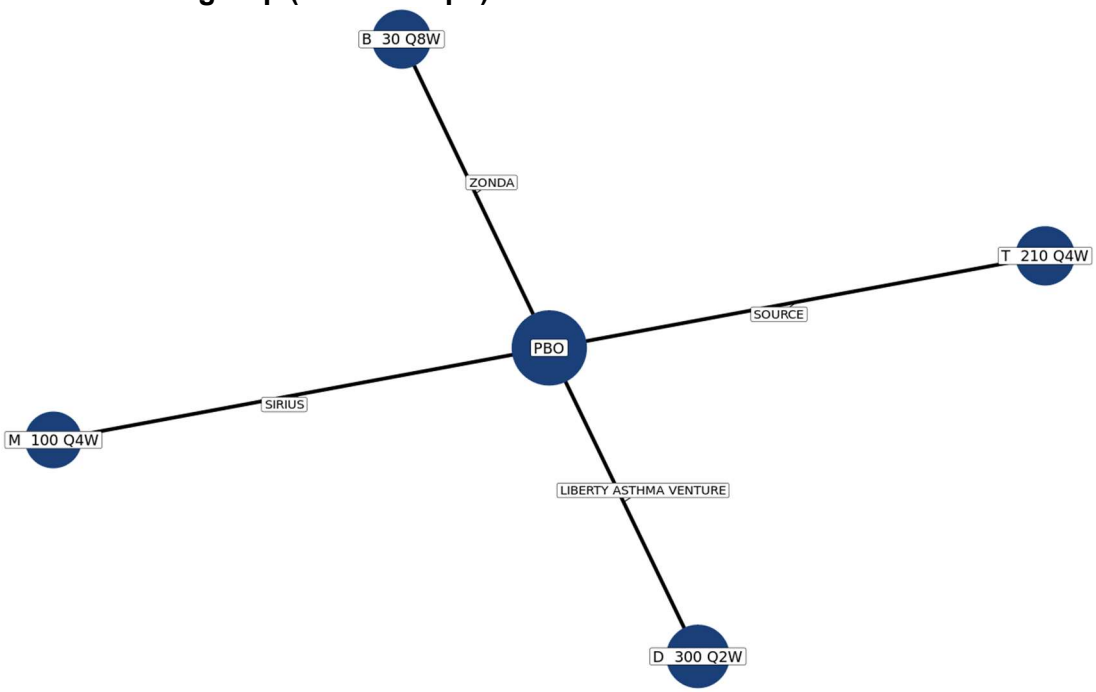
Table 88: Summary of SUCRA values from fixed effects NMA for change from baseline in OCS dose by ≥50%

Treatment	SUCRA	Probability best
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OCS, oral corticosteroid; SUCRA, surface under the cumulative ranking.
† Dupilumab 300 mg is not a NICE-recommended dose.

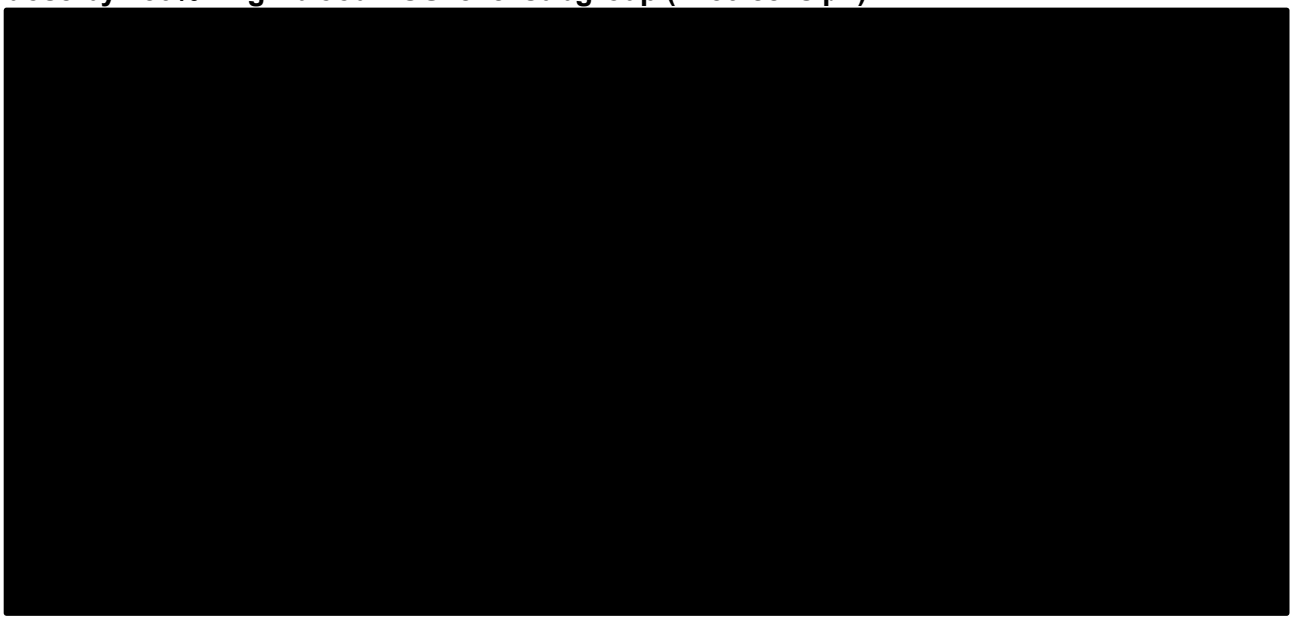
High blood EOS level (≥150 cells/μL)

Figure 56: Evidence network for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥150 cells/μL)



Abbreviations: B, benralizumab; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

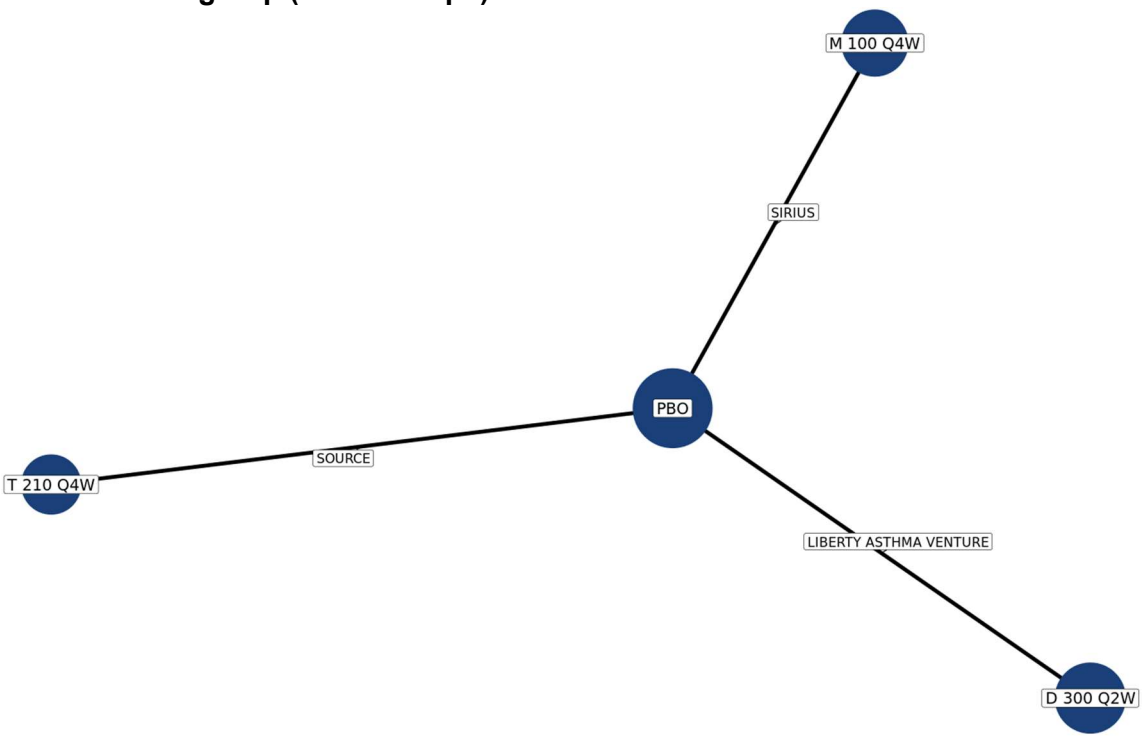
Figure 57: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥150 cells/μL)



Abbreviations: B, benralizumab; CrI, credible interval; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; 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.
Note: D 300 Q2W is not a NICE-recommended dose.

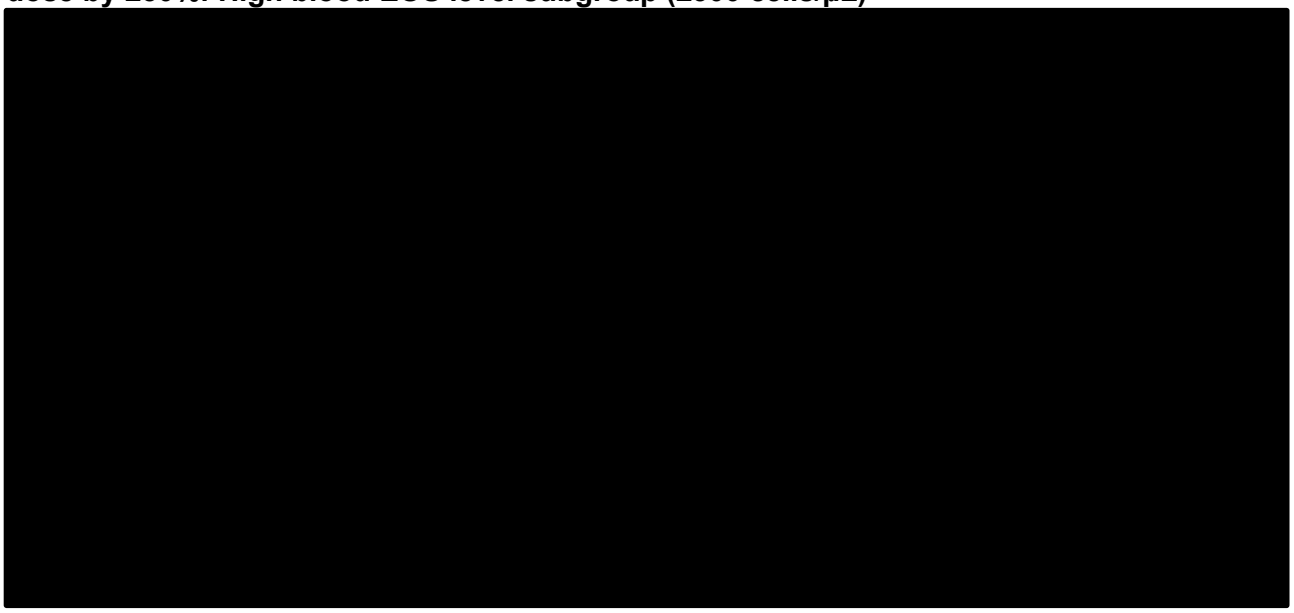
High blood EOS level (≥300 cells/μL)

Figure 58: Evidence network for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥300 cells/μL)



Abbreviations: D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

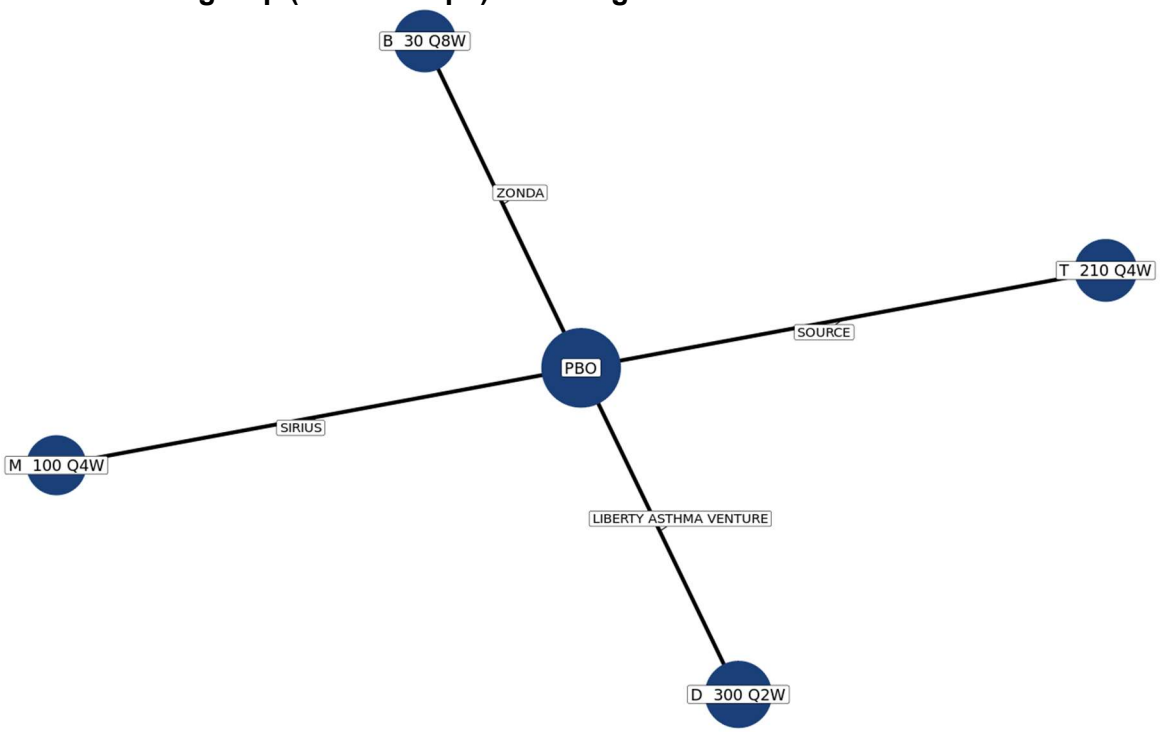
Figure 59: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥300 cells/μL)



Abbreviations: CrI, credible interval; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 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.

High blood EOS level (≥300 cells/µL) including ZONDA

Figure 60: Evidence network for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥300 cells/µL) including ZONDA



Abbreviations: B, benralizumab; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; T, tezepelumab.
Note: D 300 Q2W is not a NICE-recommended dose.

Figure 61: Pairwise comparisons from fixed effects NMA for change from baseline in OCS dose by ≥50%: High blood EOS level subgroup (≥300 cells/µL) including ZONDA

[redacted]

Abbreviations: B, benralizumab; CrI, credible interval; D, dupilumab; EOS, eosinophil; M, mepolizumab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OCS, oral corticosteroid; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 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.

B.2.9.2.4 Summary

The NMAs assessed five outcomes: reduction in AAER, reduction in AAER leading to hospitalisation, change from baseline in ACQ score, change from baseline in pre-bronchodilator FEV_1, and change from baseline in the OCS dose by predefined reduction categories. The highest ranked biologic comparators in the primary analyses of AAER, AAER leading to hospitalisation, [redacted] were tezepelumab 210 mg Q4W, tezepelumab 210 mg Q4W, omalizumab, dupilumab 200 mg Q2W, and benralizumab 30 mg Q8W, respectively.

In the reduction in AAER primary analysis, tezepelumab was ranked the most favourable treatment because it was numerically better than all other biologics (i.e. the league table showed overlapping CrIs between the pairwise combinations of the biologics indicating no significant differences). Similarly, no significant differences between biologics were observed on reduction in AAER leading to hospitalisation [redacted]

As expected, all biologics demonstrated statistically significant improvement against placebo on reduction in AAER [redacted] Of note, only tezepelumab and mepolizumab demonstrated statistically significant improvement against placebo when assessing the reduction in AAER leading to hospitalisation. [redacted].

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

The main strength of the NMAs was that they allowed evidence for tezepelumab to be indirectly compared with that for other biologics used in severe asthma and thus generate an effectiveness estimate for this comparator, as per the NICE scope. However, it should be acknowledged that the NMA are subject to the following limitations, which may create some uncertainty in the estimates derived:

B.2.9.3.1 Placebo equivalents

BSC and optimised asthma therapy were considered equivalent to placebo. This assumption was necessary to include omalizumab studies that were not placebo-controlled in the network. This assumption was tested using sensitivity analyses that excluded omalizumab studies that were not placebo-controlled for all outcomes except OCS reduction (see Section B.2.9.3.4).

B.2.9.3.2 ACQ versions

For the analyses assessing ACQ, all versions of the ACQ were assumed to be equivalent. This assumption was validated by KEEs, who suggested that all versions of the ACQ could be included in a single network.

B.2.9.3.3 General assumptions

Method-specific assumptions inherent to all NMAs were made during the analyses. These assumptions included homogeneity, exchangeability, and consistency. The exchangeability assumption in particular may have been violated in the present analysis given the observed heterogeneity in eligibility criteria and clinically important patient characteristics across included trials, as well as the nuanced differences in target populations for each biologic. The reslizumab and mepolizumab RCTs included patients with eosinophilic asthma, while the omalizumab studies included patients with allergic asthma. The tezepelumab studies did not have such inclusion criteria. Nevertheless, it is necessary to conduct NMAs as they are a widely used, replicable statistical approach to derive relative treatment effects between interventions that may not have been compared directly in RCTs, or for which both direct and indirect evidence is available for synthesis.

B.2.9.3.4 Sensitivity analysis

Please see Appendix D.

B.2.10 Adverse reactions

- 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 like 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
- The risk of severe infections with tezepelumab was low overall and either similar to (NAVIGATOR, PATHWAY) or lower than (SOURCE) that with placebo

The adverse event (AE) data presented in Section B.2.10.1 are taken from PATHWAY, NAVIGATOR, and SOURCE since these are the Phase 2 and 3 trials of most relevance to the decision problem and are used to inform the economic model.

The safety overview presented in Section B.2.10.3 is based on data from the primary safety pool, which consisted of pooled AE data from PATHWAY (tezepelumab 210 mg SC Q4W trial arm only) and NAVIGATOR. The primary safety pool included 665 subjects who received tezepelumab 210 mg SC Q4W for up to 1 year, representing approximately 640 subject-years of exposure. Key safety data from SOURCE used to support marketing authorisation of tezepelumab are also presented in Section B.2.10.3.

B.2.10.1 Studies identified in Section 2.2

B.2.10.1.1 PATHWAY

An overall summary of AEs reported during the PATHWAY trial is presented in Table 89. A summary of AEs reported in ≥5% of subjects in the total tezepelumab group (all three tezepelumab dose arms combined) is presented in Table 90. Note that unless otherwise stated, all AEs were treatment-emergent.

Overall, AEs were well balanced between the tezepelumab and placebo arms. Approximately 65% of subjects in each of the three tezepelumab arms and the placebo arm experienced one or more AEs. The majority of subjects had AEs that were Grade 1

(mild) or Grade 2 (moderate) in severity, and were considered not related to study treatment as judged by the investigator.

The proportion of subjects with at least one SAE was similar between the tezepelumab and placebo arms. One subject in the 210 mg Q4W arm had an SAE related to study treatment as judged by the investigator. Few subjects had AEs that resulted in permanent discontinuation of study treatment.

The most frequently reported AEs by preferred term were asthma, nasopharyngitis, bronchitis, and headache. Nasopharyngitis, bronchitis, and headache occurred at similar frequencies across the tezepelumab and placebo arms, whereas, as expected, asthma occurred at a greater frequency (>10% difference) in the placebo arm compared with the tezepelumab arms (Table 90).

Table 89: Overall summary of AEs reported during PATHWAY (as-treated population)

AE category, n (%)†	Tezepelumab				Placebo (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
≥1 AE	93 (67.4)	90 (65.7)	89 (65.0)	272 (66.0)	91 (65.9)
≥1 AE (≥ Grade 3 severity)‡	26 (18.8)	29 (21.2)	21 (15.3)	76 (18.4)	28 (20.3)
≥1 treatment-related AE§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (Grade 5 severity)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
≥1 SAE¶	17 (12.3)	13 (9.5)	18 (13.1)	48 (11.7)	18 (13.0)
≥1 treatment related SAE §,¶	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥1 AE resulting in permanent treatment discontinuation	0 (0.0)	2 (1.5)	3 (2.2)	5 (1.2)	1 (0.7)

Abbreviations: AE, adverse event; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse event.
† Subjects were counted once for each category regardless of the number of events.
‡ Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. Determination of severity was made by the investigator based upon medical judgement.
§ Relatedness to treatment was based on the investigator's assessment.
¶ SAE criteria included death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event and/or congenital anomaly/birth defect in the offspring of the subject.

Table 90: AEs reported in ≥5% of subjects in the total tezepelumab group of PATHWAY (as-treated population)

Preferred term, n (%)†	Tezepelumab				Placebo (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
Asthma‡	35 (25.4)	27 (19.7)	38 (27.7)	100 (24.3)	50 (36.2)

Preferred term, n (%)†	Tezepelumab				Placebo (n=138)
	70 mg Q4W (n=138)	210 mg Q4W (n=137)	280 mg Q2W (n=137)	Total (n=412)	
Nasopharyngitis	19 (13.8)	19 (13.9)	15 (10.9)	53 (12.9)	16 (11.6)
Bronchitis	8 (5.8)	5 (3.6)	9 (6.6)	22 (5.3)	7 (5.1)
Headache	6 (4.3)	11 (8.0)	5 (3.6)	22 (5.3)	6 (4.3)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse event.
† Subjects were counted once for each preferred term regardless of the number of events.
‡ The preferred term of asthma included all asthma events including protocol-defined asthma exacerbations.
MedDRA version 19.1

B.2.10.1.2 NAVIGATOR

An overall summary of AEs reported during the NAVIGATOR trial is presented in Table 91. A summary of AEs reported in >3% of subjects in either trial arm is presented in Table 92. Note that unless otherwise stated, all AEs were treatment-emergent.

The majority [redacted] of subjects experienced one or more AEs. The overall incidence of AEs was similar between the tezepelumab ([redacted] and placebo [redacted] arms. No deaths occurred during the on-treatment period in the tezepelumab or placebo arms. A total of two deaths were reported on-study in the placebo arm, which were assessed as not causally related to study treatment. SAEs were reported with a lower incidence in the tezepelumab arm [redacted] than in the placebo arm [redacted] AEs leading to discontinuation from treatment were experienced by [redacted] subjects in the tezepelumab arm and [redacted] subjects in the placebo arm (Table 91).

The most common AEs reported in the tezepelumab arm were nasopharyngitis, upper respiratory tract infection, headache, and asthma, reported [redacted] of subjects, respectively, compared with [redacted] of subjects in the placebo arm. Incidences of most AEs were generally similar across both treatment groups, except for upper respiratory tract infection and asthma, which were reported with lower incidence in the tezepelumab arm compared with the placebo arm (Table 92).

Table 91: Overall summary of AEs reported in NAVIGATOR (safety analysis set)

AE category, n (%)†	Tezepelumab (n=528)	Placebo (n=531)
Any AE	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]
Any SAE (including death)	[redacted]	[redacted]
Any AE leading to discontinuation of treatment	[redacted]	[redacted]

Abbreviations: AE, adverse event; SAE, serious adverse event.
† Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.

Table 92: AEs reported in >3% of subjects in either trial arm of 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]
[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.

B.2.10.1.3 SOURCE

An overall summary of AEs reported during the SOURCE trial is presented in Table 93. A summary of AEs reported in >3% of subjects in either trial arm is presented in Table 94. Note that unless otherwise stated, all AEs were treatment-emergent.

The overall incidence of subjects with at least one AE was [redacted]. The number of subjects with AEs related to study treatment, as judged by the investigator, [redacted] respectively. [redacted]. A total of [redacted] in

the tezepelumab arm and [redacted] in the placebo arm reported an SAE during the on-treatment period. [redacted]. AEs leading to discontinuation from treatment were experienced by a total of [redacted] (Table 93).

The most common AEs in the tezepelumab arm were [redacted]. The most common AEs in the placebo arm were [redacted] (Table 94).

Table 93: Overall summary of AEs reported in SOURCE (safety analysis set)

AE category, n (%)†	[redacted]	[redacted]
Any AE	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]
Any SAE (including events with outcome death)	[redacted]	[redacted]
Any AE leading to discontinuation of study treatment	[redacted]	[redacted]

Abbreviations: AE, adverse event.
† Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.

Table 94: AEs reported in >3% of subjects in either trial arm of 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]

Preferred term, n (%)†	[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.

B.2.10.2 Additional studies

There are no additional studies relevant for this submission.

B.2.10.3 Safety overview

The overall clinical development programme for tezepelumab included safety assessments of 1,289 subjects with asthma who received at least one dose of tezepelumab SC at doses of 70 mg Q4W, 210 mg Q4W, or 280 mg Q2W, representing approximately 1,107 subject-years of exposure. Within this group, a total of 1,104 subjects were exposed to tezepelumab doses of 210 mg SC Q4W or higher for 6 months (defined as ≥20 weeks of dosing) and 787 subjects were exposed to tezepelumab doses of 210 mg SC Q4W or higher for 1 year (≥48 weeks of dosing).

The evaluations of safety data submitted as part of the marketing authorisation application for tezepelumab and which are presented below were based on the primary safety pool. The primary safety pool consisted of pooled AE data from the confirmatory asthma exacerbation studies NAVIGATOR and PATHWAY (the 210 mg SC Q4W SC dose arm only). In total, the primary safety pool included 665 subjects who received tezepelumab 210 mg SC Q4W for up to 1 year, representing approximately 640 subject-years of exposure.

B.2.10.3.1 Adverse events and serious adverse events

Based on evaluation of AE data from the primary safety pool (NAVIGATOR and PATHWAY [the 210 mg SC Q4W SC dose arm only]), tezepelumab 210 mg SC Q4W was well tolerated in subjects with severe, uncontrolled asthma:

- The overall incidence of subjects with AEs in the on-treatment period [redacted]
- The incidence of SAEs in the on-treatment period was [redacted]

[redacted]

- The incidence of AEs leading to discontinuation of study treatment in the [redacted]
- There were [redacted]. There were [redacted]
- The majority of AEs reported for [redacted]. The incidence of AEs considered causally related to study treatment by the investigator was [redacted]
- [redacted]The four most common AEs reported in the [redacted], respectively
- The AE profile of tezepelumab was [redacted]

Based on evaluation of data from SOURCE, tezepelumab 210 mg SC Q4W was well tolerated in subjects with severe, OCS-dependent asthma:

- The overall incidence of subjects with AEs in the on-treatment period was [redacted]
- The incidence of subjects reporting SAEs during the on-treatment period was [redacted]. [redacted] was the most commonly reported SAE in both treatment groups with an incidence of [redacted], respectively. Apart from [redacted], [redacted]. [redacted]

[redacted]

- The incidence of AEs leading to discontinuation of study treatment was [redacted]
- During the on-treatment period, there was [redacted]
- The majority of AEs reported for [redacted].
  The incidence of subjects with AEs considered causally related to study treatment by the investigator was [redacted]
- The four most common AEs reported [redacted]

Overall, the AE profile for [redacted]

B.2.10.3.2 Adverse events of special interest (AESI)

In the primary safety pool, the incidence of adverse events of special interest (AESIs) in the tezepelumab arm [redacted] to the incidence of the corresponding AESIs in the placebo arm.

In the on-treatment period, 28 subjects reported SAEs in the Infections and Infestations System Organ Class ([redacted] A total of [redacted]). A total of [redacted]. Within the narrow standard MedDRA query for hypersensitivity, [redacted]).

[redacted]

In the SOURCE study, evaluation of AESIs of [redacted]. The AESI of [redacted]

Of note, across the clinical trial programme there [redacted]

B.2.10.3.3 Safety and immunogenicity

The incidence of treatment-emergent anti-drug antibodies was low in each of the individual PATHWAY, NAVIGATOR, and SOURCE trials [redacted]).

B.2.10.3.4 Adverse drug reactions

Based on a detailed assessment by an internal peer review panel of data from the confirmatory asthma exacerbation studies, pertinent information from other elements of the development programme (e.g. non-clinical information), and information from outside the tezepelumab development programme (e.g., data from the literature), few AEs were considered to have a reasonable possibility of having a causal association with tezepelumab.

Those events that AstraZeneca considered as adverse drug reactions included: arthralgia, pharyngitis (grouped term based on preferred terms of pharyngitis, pharyngitis streptococcal, pharyngitis bacterial, and viral pharyngitis), injection site reaction, and rash

(grouped term based on preferred terms of rash, rash pruritic, rash erythematous, rash maculo-papular, and rash macular). These adverse drug reactions all occurred with a frequency of ≥1/100 to <1/10 and were therefore defined as 'common'.

B.2.10.3.5 Safety in adolescents

Based on the assessment of AEs for tezepelumab compared with placebo in 82 subjects aged 12–17 years in NAVIGATOR, tezepelumab was well tolerated in adolescent subjects with an AE profile that appears similar to that in adult subjects with severe asthma. The overall incidence of AEs in adolescent subjects during the on-treatment period was similar between the tezepelumab [redacted] and placebo [redacted] arms. The most common AEs in adolescent subjects (reported in ≥5% of subjects) in the tezepelumab arm were: [redacted] The incidence of SAEs was low and similar between the tezepelumab and placebo arms ([redacted]).

B.2.10.3.6 Other safety information – clinical laboratory data, electrocardiogram (ECG), and vital signs

In PATHWAY, NAVIGATOR, and SOURCE, beyond the [redacted].

B.2.10.3.7 Conclusion

Tezepelumab 210 mg SC Q4W is well tolerated in adults and adolescents 12 years and older with severe asthma.

B.2.11 Additional and ongoing studies

An extension study, DESTINATION, assessing the safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma is ongoing (120).

A single arm Phase 3b trial, WAYFINDER, assessing the efficacy and safety of tezepelumab in reducing OCS use in adult patients with severe asthma who are receiving

OCS with or without additional asthma controlled medications is also ongoing. [redacted] (121).

CASCADE is an additional trial providing evidence for tezepelumab. This was a Phase 2, randomised, double-blind, placebo-controlled trial that evaluated the effect of tezepelumab on airway inflammation in adults with inadequately controlled moderate-to-severe asthma, taking inhaled corticosteroids and at least one additional asthma controller. A brief summary of the CASCADE trial is provided in Table 95. The CASCADE study was novel as the effect of tezepelumab on airway tissue inflammatory cells, and the broader mechanisms by which tezepelumab improves clinical asthma outcomes, had not yet been assessed in humans. Tezepelumab was shown to reduce airway hyperresponsiveness to mannitol, indicating that the TSLP blockade may have additional benefits in asthma beyond reducing T2 airway inflammation. In addition:

- Airway submucosal EOS were nominally significantly reduced ($p<0.001$) in the tezepelumab group at the end of treatment; and tezepelumab demonstrated reductions in submucosal EOS across all baseline biomarker groups
- Tezepelumab resulted in reductions in blood EOS, FeNO, serum IL-5 and IL-13, and plasma eosinophil-derived neurotoxin from baseline
- Treatment with tezepelumab resulted in a greater reduction in airway hyperresponsiveness to mannitol compared with placebo (44)

A brief summary of the CASCADE trial is provided in Table 95.

Table 95: CASCADE trial summary

Category	CASCADE study details (44)
Objective	To assess the efficacy of tezepelumab on airway inflammation in subjects with moderate-to-severe uncontrolled asthma
Trial design	• Phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel group • Subjects were randomised 1:1 to receive tezepelumab or placebo (stratified by screening blood EOS level of <150, 150 to <300 or ≥300 cells/µL) for 28 weeks
Enrolled population	Adults (N=116) aged 18–75 years with uncontrolled, moderate-to-severe asthma taking ICS and at least one additional asthma controller
Inclusion criteria	• Subjects received medium- or high-dose ICS (250–500 µg/day or >500 µg/day fluticasone DPI or equivalent) for ≥12 months at screening • Subjects received at least one additional asthma controller medication (e.g. LABA, LTRA, LAMA, cromones or theophylline), with or without mOCS, for ≥3 months at screening • Morning pre-BD FEV_1 >50% predicted normal and >1 L at screening or at the run-in visit • Historical FEV_1 reversibility of ≥12% and ≥200 mL in the 12 months before the screening or run-in visits

Category	CASCADE study details (44)
	• Study population was monitored to ensure that ~30% of patients had blood EOS of <150 cells/μL at enrolment, ~30% had 150 to <300 cells/μL and ~40% had ≥300 cells/μL
Trial treatments	• Tezepelumab 210 mg SC Q4W (n=59) • Placebo SC Q4W (n=57)
Primary efficacy endpoint	CFB in the number of airway submucosal inflammatory cells per mm² in bronchoscopic biopsy samples in the overall study population
Key secondary endpoints	• CFB in reticular basement membrane thickness and in airway epithelial integrity • CFB in the number of airway submucosal inflammatory cells per mm² in bronchoscopic biopsy samples across the spectrum of patient T2 status
Other efficacy endpoints	• CFB in biomarkers and cytokines associated with airway inflammation • Airway hyperresponsiveness to mannitol challenge • Spirometry measures of lung function • ACQ-6 • CT scan and airwave oscillometry measures of large and small airway function for further assessment of airway remodelling
Efficacy results	• Tezepelumab reduced airway hyperresponsiveness to mannitol, indicating that TSLP blockade may have additional benefits in asthma beyond reducing T2 airway inflammation • Airway submucosal EOS were significantly reduced (nominal p<0.001) in the tezepelumab group; tezepelumab demonstrated reductions in submucosal EOS across all baseline biomarker groups • Tezepelumab resulted in reductions in blood EOS, FeNO, serum IL-5 and IL-13, and plasma EDN from baseline • Treatment with tezepelumab resulted in a greater reduction in airway hyperresponsiveness to mannitol compared with placebo
Safety results	Tezepelumab was well tolerated, with no safety findings of concern
Conclusion	Tezepelumab reduced submucosal EOS counts vs placebo in bronchial biopsy samples and was associated with a reduction in T2 biomarkers, including blood EOS count and FeNO. Importantly, treatment was also associated with a reduction in airway hyperresponsiveness vs placebo

Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; BD, bronchodilator; CFB, change from baseline; CT, computed tomography; DPI, dry powder inhaler; EDN, eosinophil-derived neurotoxin; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; mOCS, maintenance oral corticosteroid treatment; Q4W, once every 4 weeks; SC, subcutaneous; TSLP, thymic stromal lymphopoietin.

B.2.12 Innovation

B.2.12.1 Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of TSLP

Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of TSLP (39). TSLP is an epithelial-derived cytokine released in response to multiple triggers associated with asthma exacerbations, such as viruses, allergens, pollutants, and other airborne irritants (39, 48, 49). When released by airway epithelial cells, TSLP initiates an

inflammatory cascade that results in eosinophilic (including allergic) inflammation, neutrophilic inflammation, and structural changes to the airway (39) (see Section B.1.3.5).

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 (42, 122, 123). 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 (39). This novel mechanism of action allows tezepelumab to deliver efficacy for severe asthma patients regardless of biomarkers or phenotype, as described in more detail in Section B.2.12.2.

B.2.12.2 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 as per the anticipated licensed indication

Existing biologics for severe asthma are limited in that they are only indicated for patients with eosinophilic or allergic phenotypes (see Table 4 in Section B.1.3.6.1). 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 or specific IgE (42, 43). Tezepelumab significantly reduced the rate of asthma exacerbations by up to 71% across all severe, uncontrolled asthma patients regardless of phenotype and irrespective of biomarker levels (42, 43) (see Section B.2.6.1.1). Furthermore, tezepelumab is the first and only biologic that has demonstrated statistically significant reductions in annual exacerbation rates for patients with EOS <300 cells/μL (Section B.2.7.1.2). Similar results were observed for patients with EOS <150 cells/μL. More details on the efficacy of tezepelumab across asthma phenotypes and biomarker profiles are provided in Section B.2.13.1.2.

B.2.12.3 Tezepelumab was granted breakthrough therapy designation by the US Food and Drug Administration (FDA) in 2018 and granted Priority Review in 2021

The observed efficacy of tezepelumab in a broad range of patients with severe asthma in PATHWAY led to it being designated a ‘breakthrough therapy’ by the US Food and Drug Administration in 2018 for patients with severe asthma without an eosinophilic phenotype, who are receiving ICS/LABA with or without OCS and additional asthma controllers (124).

In addition, tezepelumab was granted Priority Review in 2021 by the FDA (125). The FDA grants Priority Review to applications for medicines that offer significant advantages over available options by demonstrating safety or efficacy improvements, preventing serious conditions, or enhancing patient compliance (126).

B.2.12.4 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 (44). Feedback from UK clinicians (n=7) highlighted how data on airway hyperresponsiveness is an area of clinical differentiation for tezepelumab. As tezepelumab directly acts on the airway epithelia, clinicians would expect to see the failure rate of treatment to be lower as tezepelumab as result of impact on airway hyperresponsiveness and other mechanistic effects of working higher in the inflammatory cascade. Clinicians highlighted that current biologics either do not have data, or have very poor data on airway hyperresponsiveness, which is a very important endpoint in clinical practice, and a hallmark of asthma used to characterise disease diagnosis (96). This could potentially be more beneficial for patients that exhibit significant airway hyperresponsiveness.

B.2.12.5 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

Insights gathered from UK respiratory clinicians (n=7) highlighted the complexity of the reimbursement criteria for currently approved biologics (96). NICE's recommendations relate to subsets of the patient population with 3 or more exacerbations in the prior year OR who are on mOCS, and reflect the fact that existing biologics are only effective in subpopulations defined by biomarkers. NICE eligibility criteria for biologics are defined by multiple characteristics including exacerbation history, EOS level, mOCS use, FeNO level, IgE level and age. As a result, clinicians stated that often patients do not meet the eligibility

criteria (96). Therefore, biomarker requirements for reimbursement or treatment eligibility can delay treatment initiation with currently available biologics. This puts patients at risk of asthma exacerbations and may result in them needing mOCS (127).

Clinicians agree that there is value in having a biologic with a simpler and broader recommendation to allow patients not currently eligible for a biologic therapy to have access to effective biologic therapy (96). Biomarkers help determine how patients are going to respond and what is the cause of the patient's asthma, but current reimbursement criteria are too restrictive and leave out a notable proportion of patients who should be treated earlier with a biologic.

The efficacy of tezepelumab in the treatment of severe, uncontrolled asthma across phenotypes and irrespective of biomarkers is anticipated to offer simplification to the treatment pathway and enable more patients to have access to biologic therapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

B.2.13.1.1 Tezepelumab reduces the rate and severity of asthma exacerbations, including those resulting in hospitalisations or ER visits

The primary efficacy endpoint of the PATHWAY and NAVIGATOR trials was the AAER at Week 52, where an AAER reduction of at least 20–40% was considered clinically meaningful (128). Both trials met their primary endpoints, with tezepelumab treatment resulting in statistically significant reductions in exacerbation rates of 71% ($p<0.001$) and 56% ($p<0.001$) compared with the placebo at Week 52 in PATHWAY (see Section B.2.6.1.1) and NAVIGATOR (Section B.2.6.2.1), respectively. Results of the pooled PATHWAY and NAVIGATOR analysis (Section B.2.8) confirmed the results of the individual studies. In the pooled analysis, tezepelumab reduced AAER over 52 weeks by 60% compared with placebo (rate ratio: 0.40; 95% CI: 0.34, 0.48).

In the SOURCE trial, which enrolled patients with OCS-dependent severe asthma, treatment with tezepelumab reduced the rate of exacerbations over 48 weeks by a clinically meaningful 31% compared with placebo ($p=0.111$; see Section B.2.6.3.2), despite subjects also reducing their long-term OCS use over this time frame.

In addition to reducing AAER, tezepelumab was shown to reduce the rate and severity of exacerbations resulting in hospitalisations or ER visits. In NAVIGATOR, exacerbations resulting in hospitalisations or ER visits were reduced by 79% (nominal p<0.001) and the proportion of patients who experienced a severe exacerbation-related hospitalisation were reduced by 44% for tezepelumab patients versus placebo. Tezepelumab patients therefore have been shown to require less HCRU before hospitalisation and no ICU admissions compared with placebo patients (129). Similar data was also shown in PATHWAY where exacerbations resulting in hospitalisations or ER visits were reduced by 85% versus placebo (nominal p=0.005), and in SOURCE, the reduction was 41% (p=0.361). This is an important finding since healthcare resource use costs are approximately twice as high in patients with severe, uncontrolled asthma versus those with severe, controlled asthma (59, 130). Hospitalisations or ER visits for asthma increase the future risk of exacerbations and asthma-related death (102). In a 2017 UK database study of patients (N=211,807) with asthma, patients who experienced an exacerbation requiring an ER/hospital admission had a 32–35% greater risk of a subsequent exacerbation during the 12 months after the index date compared with patients experiencing exacerbations only requiring OCS treatment (58).

B.2.13.1.2 Tezepelumab reduces AAER (and associated ER visits/hospitalisations) across asthma phenotypes and irrespective of biomarkers

A key feature of tezepelumab is that, unlike current biologics, it is efficacious across the full spectrum of asthma phenotypes and biomarker profiles.

Subgroup analyses in NAVIGATOR demonstrated consistent reductions in AAER with tezepelumab versus placebo over 52 weeks irrespective of subject baseline asthma phenotype and biomarker status. Clinically meaningful reductions in AAER were observed across baseline EOS levels (nominal significance for all subgroups aside from EOS <300 cells/μL which showed statistical significance), with reductions versus placebo ranging from 39 to 77% for EOS <150 cells/μL to ≥450 cells/μL, respectively. Similarly, greater reductions in AAER with tezepelumab versus placebo were seen at 52 weeks regardless of subject allergic status (allergic: 58%; non-allergic: 51%). Furthermore, in the pooled analysis of PATHWAY and NAVIGATOR data, in the overall pooled population (N=1,334), tezepelumab reduced AAERs leading to hospitalisations and/or ER visits over 52 weeks by 79% when compared with placebo, with subgroups of subjects based on

baseline biomarkers and other demographic characteristics showing consistent results as that seen in the overall pooled population.

Tezepelumab addresses an unmet need in patients with EOS <300 cells/μL, and is the first and only biologic shown to consistently reduce AERR in the subgroup of patients with EOS <150 cells/μL. Approximately 50% of subjects enrolled in any of the PATHWAY, NAVIGATOR, and SOURCE trials had baseline EOS <300 cells/μL. The prevalence of patients with severe, uncontrolled asthma with EOS <300 cells/μL varies across studies, with estimates ranging from 43 to 78% (38, 66, 78, 79, 98). Currently approved biologics have sub-optimal efficacy in this subpopulation (39), meaning that these patients are more likely to experience persistent asthma symptoms, remain vulnerable to exacerbations and hospitalisations, and require ongoing treatment with OCS. Tezepelumab, however, was shown to be efficacious in reducing AAER in the subgroup of patients with EOS <300 cells/μL. In PATHWAY, among subjects receiving the 210 mg dose of tezepelumab and whose baseline EOS was <300 cells/μL, AAER at 52 weeks was reduced by 81% versus placebo (nominal p<0.001). Similarly, in NAVIGATOR, among subjects with EOS <300 cells/μL, a statistically significant 41% reduction in AAER versus placebo at Week 52 (p<0.001) was observed with tezepelumab versus placebo.

B.2.13.1.3 Tezepelumab improves asthma control and symptoms

In patients with severe asthma, poor asthma control is associated with higher exacerbation rates and impaired lung function (1, 19). It is also associated with a range of respiratory and non-respiratory comorbidities, including hypertension, allergy, type 2 diabetes, COPD, and chronic sinusitis, all of which add to the burden of asthma symptoms (60-64). Uncontrolled asthma is detrimental to HRQoL (55, 61, 65, 66) and results in increased healthcare costs (18, 22, 69).

The six-item Asthma Control Questionnaire (ACQ-6) measures symptoms and functions reflective of asthma control, including morning/night awakenings by symptoms, dyspnoea, wheezing, and limitations in daily activity with the possible score ranging from 0 (totally controlled) and 6 (severely uncontrolled) (2, 131). A ≥0.5-point improvement in ACQ-6 score represents a clinically meaningful improvement (131).

In all three pivotal trials, tezepelumab treatment resulted in greater improvements from baseline in ACQ-6 than placebo, with 86.25, 76.9, 65.2% of tezepelumab-treated subjects achieving clinically meaningful improvements in ACQ-6 scores in the NAVIGATOR,

PATHWAY, and SOURCE trials, respectively. In NAVIGATOR, improvement in ACQ-6 was statistically significantly greater with tezepelumab compared with placebo (p<0.001). Furthermore, 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. Improvements in asthma control with tezepelumab, as assessed by ACQ-6, are indicative of a reduction in activity limitation and interference with daily life caused by severe, uncontrolled asthma.

Asthma Symptom Diary (ASD) scores also improved with tezepelumab treatment. The ASD evaluates the severity of asthma-related symptoms (wheezing, shortness of breath, cough, chest tightness), night-time awakenings, and activity limitations via a daily diary that is completed each day in the morning and evening (6). A lower ASD score indicates improved asthma symptoms, and an individual score change of ≥0.5 is considered clinically meaningful (6).

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; see Table 38). In NAVIGATOR, the improvement in ASD between baseline and Week 52 was clinically meaningful as well as statistically significantly greater than that observed in placebo subjects (p=0.004; see Table 38). 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.

B.2.13.1.4 Tezepelumab improves lung function

Decreased lung function is associated with reduced HRQoL and can result in end-stage lung failure (132-134). Furthermore, frequent shortness of breath, wheeze, chest tightness, and cough interfere with day-to-day living, sleeping, and physical activity (102).

At Week 52 in NAVIGATOR, subjects treated with tezepelumab demonstrated a statistically significant and clinically meaningful improvement from baseline in pre-BD FEV_1 compared with placebo (0.23 L versus 0.09 L, LS mean difference: 0.13 L; 95% CI: 0.08, 0.18; p<0.001). A FEV_1 change of at least 0.1–0.2 L is considered clinically meaningful

(135). Onset of effect on pre-BD FEV_1 in NAVIGATOR was seen at the first post-baseline assessment at 2 weeks and was maintained over 52 weeks, highlighting the rapid and sustained improvement in lung function with tezepelumab treatment (see Section B.2.6.2.2). Results for FEV_1 in the PATHWAY and SOURCE trials were consistent with those observed in NAVIGATOR.

B.2.13.1.5 Tezepelumab improves patient quality of life

Results from the PATHWAY, NAVIGATOR, and SOURCE trials demonstrated that tezepelumab treatment results in rapid and sustained improvements in HRQoL.

The AQLQ(S)+12 score is a standardised quality of life measure in patients (adults and adolescents) with asthma that takes into consideration the impact of symptoms, activity limitation, emotional function, and environmental stimuli on quality of life (5). An increase in AQLQ(S)+12 score indicates improvement in HRQoL, and a score change of ≥0.5 points represents a clinically meaningful improvement (136).

For AQLQ(S)+12 total score, tezepelumab treatment resulted in a clinically meaningful improvement from baseline and a statistically significant improvement compared with placebo at Week 52 in NAVIGATOR (LS mean change from baseline 1.48 versus 1.14 in tezepelumab versus placebo groups, LS mean difference 0.33 [95% CI: 0.20, 0.47]; p<0.001); see Table 36). Furthermore, the onset of improvement in AQLQ(S)+12 was seen as early as Week 4 and was maintained to Week 52. Consistent results for AQLQ(S)+12 were observed in PATHWAY and SOURCE.

Other measures of HRQoL reported in some or all of the pivotal trials included EQ-5D-5L, St George's Respiratory Questionnaire (SGRQ), and Patient Global Impression of Change (PGI-C)/Patient Global Impression of Severity (PGI-S). In NAVIGATOR, tezepelumab improved scores and increased the percentage of subjects with no/slight impact in all five dimensions of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at Week 52 compared with placebo. At Week 24 and Week 52, the odds of achieving a clinically meaningful improvement in SGRQ – a measure of QoL in diseases of airways obstruction – were 1.79 (95% CI: 1.27, 2.52; nominal p<0.001) and 1.66 (95% CI: 1.17, 2.36; nominal p=0.05), respectively, with tezepelumab versus placebo. According to the PGI-C, a patient-reported measure of overall response to treatment, 89.6% of subjects receiving tezepelumab improved at Week 52 compared with 75.5% of patients in the placebo group. For PGI-S, a patient-reported measure of overall symptom

severity, 53.4 and 44.2% of subjects in the tezepelumab and placebo groups reported mild to no symptoms at Week 52, respectively.

In SOURCE, tezepelumab-treated subjects had a greater improvement in EQ-5D-5L visual analogue scale scores compared with placebo despite the reduction in OCS dose (LS mean difference 7.21 [95% CI: 1.01, 13.41]).

B.2.13.1.6 Tezepelumab reduces the requirement for OCS

In patients for whom biologic therapy provides inadequate disease control or who are ineligible for biologic treatment, OCS is the main treatment option (1, 26-28). Short- or long-term OCS use is associated with the risk of becoming OCS-dependent (i.e. unable to achieve asthma control without chronic OCS (72)). Acute OCS use for treatment of exacerbations is associated with adverse effects, including sleep disturbance, increased infection risk, and thromboembolism (1, 31). Cumulative overexposure to OCS can result in serious systemic adverse effects in both the short- and long-term, including osteoporosis, adrenal suppression, cardiovascular events, and diabetes (26, 28, 32-34). A key goal of treatment for severe, uncontrolled asthma, therefore, is to reduce the number of exacerbations experienced by a patient, thereby reducing – or preventing – the need for short- or long-term OCS use with the risks of adverse effects these bring.

The total number of days of exacerbation-related systemic corticosteroid (SCS) use per patient (OCS and injectable corticosteroids) was assessed as a pre-specified exploratory endpoint in the NAVIGATOR trial. Among patients with exacerbations, the mean number of days of exacerbation-related SCS use per patient was found to be numerically lower with tezepelumab (16.0 ± 25.2, n=231) compared with placebo (25.8 ± 33.9, n=319; no statistical analysis conducted). A further post-hoc analysis of exacerbation-related SCS found that, among patients who received OCS for exacerbations, the cumulative OCS dose (prednisone equivalent) was numerically lower with tezepelumab when compared with placebo (no statistical analysis conducted). Similarly, among patients with exacerbations, the mean total OCS dose (prednisone-equivalent) per patient was numerically lower with tezepelumab (425.4 ± 618.6, n=220) compared with placebo (693.3 ± 923.9, n=303; no statistical analysis conducted). Tezepelumab may therefore be associated with both fewer exacerbations and lower OCS use per exacerbation than placebo, offering additional potential benefits for patients with severe, uncontrolled asthma (130).

The primary endpoint of the SOURCE trial was the categorised percent reduction from baseline in the daily OCS dose at Week 48 without loss of asthma control. The OCS reduction categories were ≥90 to ≤100% reduction, ≥75 to <90% reduction, ≥50 to <75% reduction, >0 to <50% reduction, and no change or any increase. The odds of reaching a category of greater percentage OCS reduction were numerically higher with tezepelumab compared with placebo, with a cumulative OR of 1.28 (p=0.434; see Section B.2.6.3.1), but this did not reach statistical significance. Nevertheless, a substantial proportion of patients in the tezepelumab (54.1%) arm achieved ≥90% reduction in OCS dose (in the placebo arm, the proportion was 46.1%), suggesting that, by reducing exacerbations, tezepelumab may be able to eliminate or minimise OCS use in patients who are currently on long-term OCS.

A discussion of the reasons why SOURCE did not achieve its primary efficacy outcome is provided in Section B.2.13.2.1.

B.2.13.1.7 In indirect treatment comparisons with comparator biologics, tezepelumab is the highest ranked treatment for reduction in AAER and for reduction in AAER leading to hospitalisation

In the ITCs described in Section B.2.9, the efficacy and safety of tezepelumab in the treatment of patients with severe, uncontrolled asthma was compared against that for benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab. In the primary analyses for reduction in AAER and reduction in AAER leading to hospitalisation, tezepelumab was the numerically highest ranked biologic (although differences between treatments were not statistically significant), meaning tezepelumab treatment was numerically more likely to achieve reductions in AAER and exacerbations leading to hospitalisation than comparator biologics.

B.2.13.1.8 Tezepelumab is well tolerated in patients with severe asthma, demonstrating a similar safety profile to optimised standard of care alone

Based on the evaluation of AE data from the primary safety pool (NAVIGATOR and PATHWAY; see Section B.2.10.3), which included 665 subjects who received tezepelumab 210 mg SC Q4W for up to 1 year, representing approximately 640 subject-years of exposure, tezepelumab treatment was well tolerated in subjects aged 12 years and older with severe, uncontrolled asthma.

- The overall incidence of subjects with AEs in the on-treatment period was similar between the tezepelumab and placebo arms (74.6 versus 76.5% of subjects, respectively)
  - The four most common AEs reported in the tezepelumab arm were nasopharyngitis (19.5%), upper respiratory tract infection (9.3%), headache (7.8%), and asthma (7.4%); in comparison, incidences of subjects with these AEs in the placebo arm were 19.1, 13.3, 7.5, and 15.7%, respectively
- The incidence of SAEs in the on-treatment period was 8.6% in the tezepelumab arm and 13.0% in the placebo arm (asthma was the most commonly reported SAE in both trial arms, with an incidence of 2.3% and 6.9%, respectively)
- The incidence of AEs leading to discontinuation of investigational product in the tezepelumab and placebo arms was 2.0% and 3.0%, respectively

Tezepelumab 210 mg SC Q4W was also well tolerated among subjects with severe, OCS-dependent asthma enrolled in SOURCE.

- The overall incidence of subjects with AEs in the on-treatment period was 71.6% in the tezepelumab arm and 85.5% in the placebo arm
  - The four most common AEs reported in the tezepelumab arm were nasopharyngitis (14.9%), upper respiratory tract infection (12.2%), asthma (9.5%), and bronchitis bacterial (8.1%); in comparison, incidences of subjects with these AEs in the placebo arm were 25.0, 9.2, 17.1, and 9.2%, respectively
- The incidence of SAEs in the on-treatment period was 14.9% in the tezepelumab arm and 21.1% in the placebo arm (asthma was the most commonly reported SAE in both trial arms with an incidence of 2.7 and 10.5% respectively)
- The incidence of AEs leading to discontinuation of investigational product in the tezepelumab and placebo arms was 2.7 and 2.6%, respectively

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

B.2.13.2.1 Contextualising results from the SOURCE trial

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. Treatment with tezepelumab improved other efficacy parameters (including the number and rate of exacerbations and pre-BD FEV_1) in line with those observed in NAVIGATOR.

The following points may have played a role in the observed overall SOURCE OCS reduction results:

- A strong placebo response rate was seen in SOURCE. The proportion of patients in the placebo arm with successful categorised percent reduction in OCS dose was substantially higher than was anticipated based on previous OCS-reduction studies with biologics (137). In the published studies for mepolizumab (SIRIUS) (112), benralizumab (ZONDA) (138), and dupilumab (VENTURE) (139), only 19%, 20%, and 39% of patients assigned to placebo were able to reduce OCS by ≥75%, respectively. [redacted]
- The 36-week OCS dose reduction period in SOURCE was considerably longer than the 16-week (VENTURE and SIRIUS) or 20-week (ZONDA) period used in other studies. [redacted]
- Protocol guidance in SOURCE strongly encouraged investigators to continue OCS down-titration despite periodic worsening of asthma. Further dose reductions were allowed following asthma exacerbations in the SOURCE trial. Therefore, patients receiving placebo were given the opportunity to continue to down-titrate their OCS dose despite a higher exacerbation rate than those treated with tezepelumab. With respect to other published studies, down-titration was also permitted in SIRIUS after asthma exacerbations; however, no further down-titration could occur after an exacerbation in ZONDA, and in VENTURE, and no further dose reductions could occur after a second exacerbation. This was investigated further via a post hoc analysis (see below).
- [redacted]Patients with non-eosinophilic asthma may have a poor response to corticosteroids (95) and thus may be more readily able to reduce their daily OCS dose. However, OCS is known to suppress EOS counts meaning that EOS counts are not comparable between

patients treated and not treated with OCS (140) [redacted]

[redacted] By contrast, ZONDA included no patients with baseline EOS <150 cells/μL, and approximately 85% had baseline EOS ≥300 cells/μL (median baseline EOS: 437 cells/μL) (138). In VENTURE, 28.6% of patients had EOS <150 cells/μL and 42.4% had EOS ≥300 cells/μL (mean baseline EOS: 347 cells/μL) (139). [redacted]

[redacted]

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 (96).

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 (96).

B.2.13.2.2 PATHWAY, NAVIGATOR, and SOURCE were methodologically robust

PATHWAY, NAVIGATOR, and SOURCE were large, randomised, multinational, double-blind, placebo-controlled, well-conducted, methodologically robust clinical trials.

Randomisation to tezepelumab or placebo was achieved via a central IWRS, and packaging and preparation of investigational products was undertaken by an independent product manager (e.g. a pharmacist or study nurse) to ensure all sponsor and investigational site staff were blinded with regard to the treatment administered.

Subject baseline demographic and disease characteristics were balanced between trial arms and efficacy analyses were based on the ITT population (PATHWAY) or the FAS (NAVIGATOR/SOURCE). Trial endpoints included asthma exacerbation rate, OCS dose reduction, lung function, and various PROs, all of which were selected for their clinical relevance and acceptability by global health authorities (68).

B.2.13.2.3 NAVIGATOR and SOURCE trial results were subject to strict hierarchical statistical testing

A hierarchical testing strategy was used in the NAVIGATOR and SOURCE trials in order to test for superiority of tezepelumab over placebo in the primary and secondary efficacy endpoints while also controlling the overall Type 1 error rate at 0.05 (2-sided). Similarly, in PATHWAY, the primary efficacy endpoint was tested using a stepdown method for the three hypotheses (high dose to the medium dose to the low dose) to maintain the overall Type 1 error rate at 0.1 (2-sided).

A key strength of the NAVIGATOR trial was that all endpoints in the pre-specified hierarchical testing strategy, ordered by clinical relevance, met statistical significance. SOURCE did not achieve its primary efficacy endpoint of a statistically significant categorised percent reduction in daily OCS dose with tezepelumab versus placebo. The likely reasons for this include the strong placebo response observed in the trial, the long duration of the OCS dose reduction period, and the trial guidance strongly encouraging investigators to continue OCS down-titration despite periodic worsening of asthma. These factors are discussed in detail in Section B.2.13.2.1.

B.2.13.2.4 The pivotal trials provide efficacy and safety data of direct relevance to the anticipated licence for tezepelumab

NAVIGATOR and SOURCE provide key pivotal efficacy and safety data for the use of tezepelumab 210 mg SC Q4W in addition to standard of care from a total of 605 subjects with severe, uncontrolled asthma. (A further 137 subjects in the tezepelumab 210 mg arm of PATHWAY received tezepelumab treatment equivalent to that administered in NAVIGATOR and SOURCE). These subjects all received tezepelumab treatment in line

with the draft SmPC posology (see Appendix C) and as per its anticipated use in clinical practice.

B.2.13.2.5 Subject characteristics were reflective of those seen in patients in England

Subjects enrolled in the PATHWAY, NAVIGATOR, and SOURCE trials were broadly reflective of severe asthma patients seen in clinical practice in England (70, 73). The majority of enrolled subjects (~60%) were female, 50–60% had baseline EOS <300 cells/μL, and 40–75% had experienced two exacerbations in the 12 months prior to enrolment (see Section B.2.3.3).

While none of the randomised subjects PATHWAY, NAVIGATOR, and SOURCE were from the United Kingdom, the subgroup analysis of the primary efficacy outcome in each trial suggested there was little to no effect of subject ethnicity or geographic region on tezepelumab treatment response.

B.2.13.2.6 The endpoints used in the pivotal trials for tezepelumab are clinically relevant

The endpoints used in the PATHWAY, NAVIGATOR, and SOURCE trials were selected based on their clinical relevance in the treatment of patients with severe asthma as well as their acceptability to global health authorities (75).

Exacerbations

Asthma exacerbations are an important endpoint in clinical trials of treatments for severe asthma as they are the fundamental manifestation of asthma that is uncontrolled. Asthma exacerbations are distressing to patients and their families and can be life-threatening (45, 56). Asthma exacerbations leading to hospitalisations and ER visits greatly increase the cost of treating severe asthma (18, 22). Furthermore, asthma exacerbations that result in hospitalisations and/or ER visits considerably increase the risk of subsequent exacerbations. In a 2017 UK database study of patients (N=211,807) with asthma, patients who experienced an exacerbation requiring an ER/hospital admission had a 32–35% greater risk of a subsequent exacerbation during the 12 months after the index date compared with patients experiencing exacerbations only requiring OCS treatment (58). AAER was thus selected as the primary efficacy endpoint of the PATHWAY and NAVIGATOR trials, and was the key secondary efficacy endpoint of SOURCE. RCTs of

the comparator biologics benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab also included AAER as the primary efficacy endpoint (114, 115, 141-146).

Secondary efficacy endpoints

Secondary endpoints in the PATHWAY, NAVIGATOR, and SOURCE trials included pulmonary function (pre-BD FEV_1) and PROs, including AQLQ(S)+12, asthma control (ACQ-6), and asthma symptoms (asthma symptom score in PATHWAY and ASD in NAVIGATOR and SOURCE). These endpoints are all well-accepted in trials of patients with severe asthma and are consistent with those used in the comparator biologic pivotal trials.

Asthma control

Asthma control is an important endpoint as it is a composite measure of asthma exacerbations and asthma symptoms. In the tezepelumab trials, ACQ-6 (see Table 1) was used to measure asthma control. ACQ-6 is widely adopted as a clinical trial endpoint and has demonstrated reliability, validity, and sensitivity to changes occurring in the level of asthma control (147). It is recommended for use by the BTS/SIGN guidelines (47), and closely aligns with GINA guideline definitions of asthma control (147).

OCS dose reduction

Prolonged OCS use in patients with OCS-dependent asthma is associated with serious systemic adverse effects in both the short- and long-term, including osteoporosis, adrenal suppression, cardiovascular events, and diabetes (26, 28, 32-34) all of which increase the burden of uncontrolled asthma for patients and healthcare systems (1, 35, 36). OCS dose reduction is therefore a clinically relevant endpoint for inclusion in clinical trials of treatments for severe asthma. OCS dose reduction was the primary efficacy endpoint of the SOURCE trial and was also the primary endpoint of RCTs for benralizumab, dupilumab, and mepolizumab (148-150).

B.2.13.2.7 Conclusion

For patients with severe, uncontrolled asthma, specialist treatments, including add-on biologic therapies, are recommended, with the goal of treatment being to reduce exacerbations and dependency on OCS, and improve asthma control (47).

The inflammatory cascade of severe uncontrolled asthma is complex and heterogeneous. Current biologic agents mostly act on a single specific downstream inflammatory target like eosinophils (EOS), IgE, or cytokines (IL-4, -5 or -13) (37, 38) and have demonstrated

effectiveness only in specific phenotypes of severe asthma defined by biomarker criteria (EOS ≥300: benralizumab, mepolizumab and reslizumab; IgE: omalizumab; FeNO ≥25 and EOS ≥150: dupilumab). Accordingly, in England and Wales, NICE's recommendations on the use of biologic therapies relate to subsets of the patient population with 3 or more exacerbations in the prior year OR who are on mOCS, reflecting the fact that existing biologics are only effective in subpopulations defined by biomarkers (86, 88, 90, 92, 94).

While existing biologic agents, can be life-changing for those patients that are eligible to receive treatment, the full set of biological mechanisms driving a patient's asthma are unlikely to be addressed by currently recommended biologics (39). Furthermore, patients who regularly exacerbate but do not exhibit the NICE biomarker criteria do not have access to biologic therapy.

A significant unmet need exists for a first-line biologic treatment with efficacy across phenotypes and biomarker profiles, to enable more patients with severe, uncontrolled asthma to achieve disease control and reduce the frequency of exacerbations, hospitalisations, and OCS use.

Tezepelumab is a first-in-class biologic which acts at the top of the asthma inflammatory cascade, blocking the activity of multiple downstream pathways therefore demonstrating efficacy in severe asthma patients across multiple phenotypes and irrespective of baseline levels of currently established biomarkers, EOS, FeNO, or specific IgE (42, 43).

In the PATHWAY Phase 2 trial, tezepelumab, when compared with placebo, significantly reduced the rate of asthma exacerbations by up to 71% across all severe, uncontrolled asthma patients regardless of phenotype and irrespective of biomarker levels (42, 43). In the Phase 3 NAVIGATOR trial, tezepelumab treatment resulted in a 79% reduction in the annualised rate of exacerbations associated with an ER visit compared with placebo and an 85% reduction in exacerbations resulting in hospitalisation. Although the OCS dose reduction primary endpoint in SOURCE was not met (for the reasons described in Section B.2.13.2.1), secondary endpoint results related to exacerbations, lung function, and PROs were consistent with those of NAVIGATOR and PATHWAY: compared with placebo, AAER was reduced FEV_1 improved, asthma control (ACQ-6) and quality of life (AQLQ(S)+12) improved, and asthma symptoms (ASD) decreased, all while subjects were reducing their mOCS dose.

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 those patients who are currently ineligible and provide an additional treatment option for patients who are currently eligible for biologic treatment.

B.2.13.3 End of life

Not applicable for the indication included in this submission.

B.3 Cost effectiveness

SUMMARY

- A de novo economic model was developed to assess the cost-effectiveness of tezepelumab as an add-on to standard of care (SoC) treatment in 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 to take account of NICE's recommendations in appraisals conducted for biologic treatments:
  - Anti-IL-5 eligible (benralizumab and mepolizumab)
  - Dupilumab eligible
  - Omalizumab eligible
  - Non-bio eligible (3+ exacerbations OR mOCS)
- In the fully incremental analyses for anti-IL-5 eligible patients, tezepelumab (at the PAS price) was associated with the highest quality-adjusted life years (QALYs) and lowest costs. Tezepelumab therefore, strictly dominated all comparators
- Tezepelumab was dominant versus dupilumab (list price), with QALY gains of [redacted] and cost savings of [redacted] in the dupilumab NICE-recommended population
- Tezepelumab was dominant versus omalizumab (list price), with QALY gains of [redacted] and cost savings of [redacted] in the omalizumab NICE-recommended population
- Versus SoC, tezepelumab was associated with an incremental cost of [redacted] and a QALY gain of [redacted], resulting in an ICER of £29,968 per QALY gained
- Results of probabilistic sensitivity analysis (PSA) were 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. The ICER vs. SoC in biologic ineligible patients remained <£30,000
- The economic analysis shows that tezepelumab, as an add-on to SoC treatment, can be considered a dominant treatment option (comparator list prices) versus other biologics on their NICE-recommended populations and cost-effective versus SoC in biologic ineligible patients
- The economic model is conservative for tezepelumab, in that it underpredicts real world mortality and does not capture all elements that may influence HRQoL and costs

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify cost-effectiveness studies of relevant interventions for the treatment of people aged 12 years or older with severe asthma that is inadequately controlled by standard therapy.

The SLR searches were originally conducted on November 6th 2017, and updated on November 23rd 2021. Full details of the SLR search methodology are provided in Appendix G.

In total across the original and update SLR, three cost-effectiveness evaluations on two unique studies conducted in the UK were eligible for inclusion (151-153). Hand searching yielded an additional 10 UK health technology assessment (HTA) submissions. This resulted in a total of 13 relevant full publication studies for final inclusion in the cost-effectiveness evaluation SLR (86, 88, 90, 92, 94, 151-158). The following HTAs were included in the review:

- NICE TA278 (2013): Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation (86)
- NICE TA479 (2017): Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids (88)
- NICE TA431 (2017): Mepolizumab for treating severe eosinophilic asthma (154)
- NICE TA565 (2019): Benralizumab for treating severe eosinophilic asthma (90)
- NICE TA671 (2021): Mepolizumab for treating severe eosinophilic asthma (92)
- NICE TA751 (2021): Dupilumab for treating severe asthma with type 2 inflammation (94)
- SMC 1233 (2017): Reslizumab 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 (155)
- SMC 2139 (2019): Mepolizumab as add-on therapy for children (6y+), adolescents, and adults with severe refractory eosinophilic asthma (157)
- SMC 2155 (2019): Benralizumab as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists (156)
- SMC 2317 (2021): Dupilumab 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 fractional exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment (158)

Table 96 summarises the three cost-effectiveness evaluations identified during the SLR.

Table 96: Overview of the three cost-effectiveness evaluations identified in the SLR

Citation, country	Summary of model	Intervention/ comparator	Patient population	Source of efficacy/cost/ utility data	Base case costs [currency, year]	Base case health outcomes	Base case ICER
Johansson 2006 (152) UK, Italy, France, Germany (UK data extracted only)	Poisson regression model was used to calculate severe exacerbation rates Time horizon, NR Perspective, Societal Cycle length, NR Discounting/ benefit costs were not applied Health states NR	Budesonide/ formoterol (Symbicort) vs salmeterol/fluticasone (Seretide)	Patients with asthma who had been using ≥500 µg/day of budesonide or fluticasone (or ≥1000 µg/day of another ICS) for at least 1 month, who had experienced one or more severe exacerbations in the previous year Severe exacerbation defined as: deterioration in asthma requiring any one of the following: hospitalisation or ER treatment; OCS treatment for at least 3 days; or an unscheduled visit requiring a change in asthma treatment	**Efficacy** Based on a 12-month multinational, randomised, open-label study by Vogelmeier et al (study SD-039-0691) **Costs** Unit costs were taken from appropriate national official price lists	Costs specific to severe asthma are not reported	Severe exacerbation rate specific to the UK are not reported	ICER for Symbicort (SMART) vs Seretide (SFC) Mean direct cost per severe exacerbation avoided SMART dominant over SFC (95% CI; -12,183, -293) Mean total cost per severe exacerbation avoided SMART dominant over SFC (95% CI; -9,582, 412)
Norman 2013 (153) (list price analysis)	List price analysis	Omalizumab add-on therapy to optimised	Patients uncontrolled at step 4, and in the process of	**Efficacy** Exacerbation rates and asthma-related	**Mean costs [£, 2010]** *Adults/adolescents (≥ 12 years): age at model entry, 43 years*	**Mean QALY** *Adults/adolescents (≥ 12 years): age at model entry, 43 years*	**ICER [cost/QALY]** *Adults/adolescents (≥ 12*

Citation, country	Summary of model	Intervention/ comparator	Patient population	Source of efficacy/cost/ utility data	Base case costs [currency, year]	Base case health outcomes	Base case ICER
[This analysis formed part of the NICE MTA appraisal of omalizumab (TA278]	Markov model Time horizon, lifetime (age 100 years) Perspective, Payer (UK NHS) Cycle length, 3 months Discounting costs and QALYs: 3.5% Health states Day-to-day asthma symptoms ± omalizumab Asthma death Other cause death Clinically significant severe exacerbation Clinically significant non-severe exacerbation	standard step 4 or 5 GINA therapy vs Standard step 4 or 5 GINA therapy	moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy	mortality rates obtained from INNOVATE, IA-05 EUP, and de Vries (2010) **Costs** Therapy costs, standard care costs, and exacerbation costs taken from manufacturer's submission to NICE. **Utilities** Day-to-day asthma symptoms taken from EXALT RCT Exacerbations from Lloyd 2007	• Omalizumab, £72,938 • Standard therapy, £33,218 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, £92,497 • Standard therapy, £40,218	• Omalizumab, 14.13 • Standard therapy, 13.66 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, 17.39 • Standard therapy, 16.72	*years): age at model entry, 43 years* • Omalizumab vs standard therapy, £83,822 *Children (6-11 years): age at model entry, 9 years* • Omalizumab vs standard therapy, £78,009

Citation, country	Summary of model	Intervention/ comparator	Patient population	Source of efficacy/cost/ utility data	Base case costs [currency, year]	Base case health outcomes	Base case ICER
Faria 2014 (151) (PAS analysis) [Analysis by Faria considered cost-effectiveness under the PAS discounted price] UK	PAS analysis Markov model Time horizon, lifetime (age 100 years) Perspective, Payer (UK NHS) Cycle length, 3 months Discounting costs and QALYs: 3.5% Health states Day-to-day asthma symptoms ± omalizumab Asthma death Other cause death Clinically significant severe exacerbation Clinically significant non-	Omalizumab add-on therapy to optimised standard step 4 or 5 GINA therapy vs Standard step 4 or 5 GINA therapy	Patients uncontrolled at step 4, and in the process of moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy	**Efficacy** Exacerbation rates and asthma-related mortality rates obtained from INNOVATE, IA-05 EUP, and de Vries (2010) **Costs** Therapy costs, standard care costs, and exacerbation costs taken from manufacturer's submission to NICE. Details of the discounted PAS price considered in Faria 2014 are confidential. **Utilities** Day-to-day asthma symptoms taken from EXALT RCT	**Mean costs [£, 2010]** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, £60,406 • Standard therapy, £33,153 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, £76,386 • Standard therapy, £40,575	**Mean QALY** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, 14.14 • Standard therapy, 13.66 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, 17.39 • Standard therapy, 16.72	**ICER [cost/QALY]** *Overall population* • ≥ 12 years, £57,557 • 6-11 years, £53,348 *Hospitalisation subgroup* • ≥ 12 years, £31,782 • 6-11 years, £30,109 *Maintenance OCS subgroup* • ≥ 12 years, £34,386 *≥3 exacerbations* • ≥ 12 years, £53,087 • 6-11 years, £48,537

Citation, country	Summary of model	Intervention/ comparator	Patient population	Source of efficacy/cost/ utility data	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	severe exacerbation			Exacerbations from Lloyd 2007			

Abbreviations: CI, confidence interval; OCS, oral corticosteroid; GINA, Global Initiative for Asthma; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; MTA, multiple technology appraisal; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PAS, patient access scheme; QALY, quality-adjusted life year; SLR, systematic literature review.

B.3.2 Economic analysis

Since none of the cost-effectiveness evaluations identified by the cost-effectiveness SLR included tezepelumab as a comparator, a de novo economic model was developed for this submission.

B.3.2.1 Patient population

The economic evaluation assessed the cost-effectiveness of tezepelumab as an add-on to SoC treatment 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. The stratification is outlined in Table 97.

Table 97: Indicated and modelled patient populations for comparators included in the model

Comparator†	Licensed population	Modelled population and definition	Modelled dosage	Comment
Benralizumab + SoC	Patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA (90)	**IL-5 eligible** Age 18+: 300+ EOS (4+ Exacs OR mOCS) OR (400+ EOS AND 3 Exacs)	30 mg Q4W for the first three doses, and then Q8W thereafter	Modelled population aligns with NICE recommended populations for benralizumab and mepolizumab
Mepolizumab + SoC	Patients with severe refractory eosinophilic asthma aged 6 years and older (92, 154)		100 mg Q4W (age 12+)	
Omalizumab + SoC	Patients 6 years and older 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 ICS, plus LABA. Patients 12 years of age and older must have reduced lung function (FEV_1 <80%) (86)	**Omalizumab eligible** Age 12+: 30+ IgE AND (4+ Exacs OR mOCS)	75 to 600 mg every 2 or 4 weeks; dose and frequency determined by IgE level before the start of treatment, and body weight (kg)	Modelled population aligns with NICE recommended population for omalizumab, in the context of tezepelumab licensed population (age 12+)
Dupilumab + SoC	Patients 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment (94)	**Dupilumab eligible** 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	400 mg (two 200 mg injections) followed by 200 mg given every other week	Modelled population aligns with NICE recommended population for dupilumab (pertaining to first line biologic treatment. NICE recommendation pertains to the stated dosing regimen only. A higher dosing regimen, consisting of 600 mg (two 300 mg injections) followed by 300 mg given every other week is also licensed for severe asthma but is not NICE recommended

Comparator†	Licensed population	Modelled population and definition	Modelled dosage	Comment
SoC alone (defined as high-dose ICS and at least one additional controller medication, with or without mOCS	NA	**Non-bio eligible (3+ exacs OR mOCS)** Age 12+ AND 3+ Exacs OR mOCS minus anti-IL-5 eligible minus omalizumab eligible minus dupilumab eligible‡	See Section B.3.5.1.	Residual 3+ Exacs OR mOCS patients, who are not currently eligible for biologic treatment
Sum of modelled populations		(Label NA) Age 12+ AND 3+ Exacs OR mOCS	NA	Totality of modelled populations

Abbreviations: EOS, eosinophil; Exacs, exacerbations (in prior year); FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta agonist; mOCS, maintenance oral corticosteroid treatment; NA, not applicable; NICE, National Institute for Health and Care Excellence; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneous; SoC, standard of care.
† AstraZeneca estimates the market share of reslizumab to be approximately 0.2%. Whilst AstraZeneca fully expects tezepelumab + SoC to be cost-effective when compared with reslizumab + SoC, omitting it as a comparator negates the need for the inclusion of a further post hoc subgroup in economic modelling. Please see Section B.3.2.3.2 for further details.
‡ For the full definition of this subgroup of patients, please see Appendix Q.

B.3.2.2 Model structure

B.3.2.2.1 Base case model structure and health states

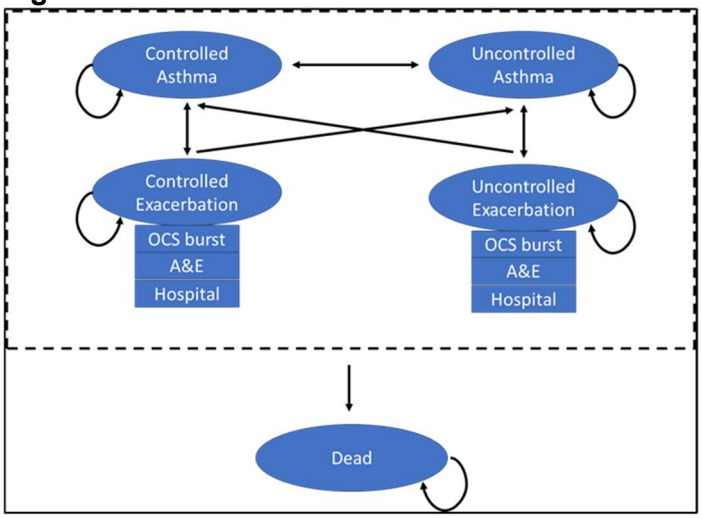
As described in Section B.1.3.2, asthma control is assessed on the basis of symptom control and future risk of exacerbations requiring a short course of OCS treatment or hospitalisation (1, 52). In general, patients with poorly controlled asthma experience greater symptom burden, lower quality of life, and are at higher risk of exacerbations than those whose asthma is controlled (55, 58, 59, 61, 65, 66). Exacerbations are costly events that may result in hospitalisation and substantially reduced quality of life (45, 56, 159). Given this clinical situation, the economic model was designed to capture the impact of both asthma control and exacerbation events explicitly.

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:
  - OCS burst: Burst of OCS for at least three consecutive days
  - A&E: An emergency room or A&E visit
  - Hospital: Hospitalisation
- Controlled/Uncontrolled exacerbation: 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 62.

Figure 62: Model structure

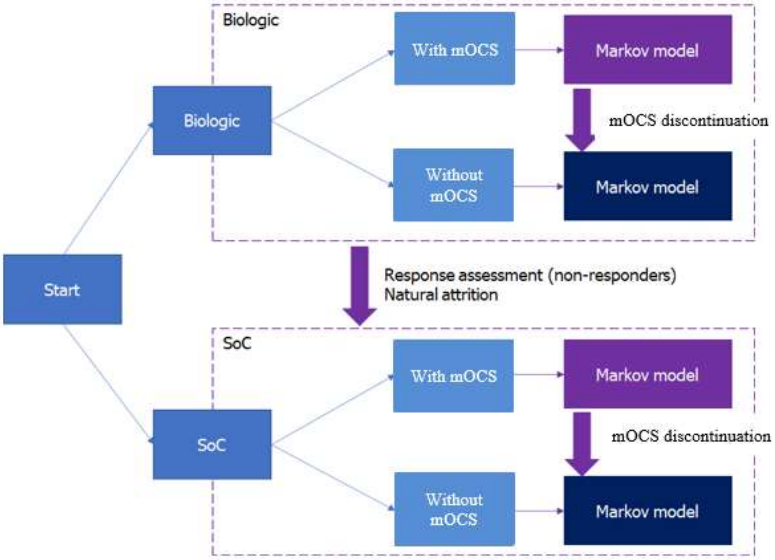


Abbreviations: A&E, Accident and Emergency; OCS, oral corticosteroid.

B.3.2.2.2 Patient flow through the model

Patient flow through the model is outlined in Figure 63. For each subgroup, patients entered the model with uncontrolled asthma, either via a biologic arm or SoC, and with mOCS use defined by the subgroup's specific baseline characteristics (receiving or not receiving mOCS). The model structure remained the same for all biologic arms and mOCS use status. Patients who entered the model on a biologic could transition to SoC only through either natural attrition (discontinuation) or via a response assessment where non-responders could discontinue biologics at a particular timepoint (see Section B.3.2.2.3). Patients could also transition from 'with mOCS' to 'without mOCS' through mOCS sparing/discontinuation.

Figure 63: Patient flow through the model



Abbreviations: mOCS, maintenance oral corticosteroid treatment; SoC, standard of care.

B.3.2.2.3 Response assessment

The model contained the functionality to assess patient response to biologic therapies. Patients who responded to treatment had a lower rate of exacerbations, whereas those who did not respond, discontinued treatment with biologic therapy and were assumed to have the same efficacy profile of SoC.

Although patients could discontinue biologic treatment at any point, in clinical practice, response to treatment is often assessed by the clinician at pre-defined timepoints. This was assumed in the model to occur at 52 weeks, in accordance with clinical expert advice and in keeping with current NICE recommendations for mepolizumab (92), reslizumab (88), benralizumab (90), and dupilumab (94). 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.*

B.3.2.2.4 Time horizon and cycle length

The model base case used a lifetime time horizon (60 years) to reflect the chronic nature of asthma, which requires interventions (including tezepelumab and other biologics) to be used over a patient's entire lifespan.

The model cycle length was 4 weeks in line with the frequency of assessments in the NAVIGATOR and SOURCE trials.

B.3.2.2.5 Perspective and discounting

The perspective of the model base case was that of the NHS and Personal Social Services (PSS) in England. For base case, costs and outcomes (life years [LYs] and QALYs) were discounted at 3.5% in line with the NICE Guide to the Methods of Technology Appraisal 2013 (160). A discount rate of 1.5% for costs and outcomes was explored in scenario analysis.

B.3.2.2.6 Model outcomes

The results of the model were expressed as an incremental cost-effectiveness ratio (ICER), in terms of incremental cost per quality-adjusted life-year (QALY) and as incremental cost per LY gained.

The features of the economic analysis in comparison to previous TAs conducted in this disease area are shown in Table 98.

Table 98: Features of the current economic analysis compared with previous appraisals

	Previous appraisal						Current appraisal	
Factor	**TA565 Benralizumab**	**TA751 Dupilumab**	**TA431 Mepolizumab**	**TA671 Mepolizumab**	**TA278 Omalizumab**	**TA479 Reslizumab**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Lifetime	1 year	Lifetime	Lifetime	Lifetime	Asthma a chronic condition with interventions used over a patient's lifetime. Lifetime horizon is long enough to capture all important differences in costs or outcomes between treatments.
Cycle length	2 weeks	4 weeks	4 weeks	NA	First cycle: 16 weeks Second cycle (children): 8 weeks Second cycle (aged ≥12 years): 10 weeks, subsequent cycles 3 months	4 weeks	4 weeks	Consistent with frequency of measurement in trials
Model approach	Markov	Markov	Markov	Cost comparison	Markov	Markov	Markov	Aligns with previous NICE submissions for comparator biologics. The Markov approach allows for capture of the impact of both asthma control and exacerbation events explicitly on incremental costs and QoL benefits

	Previous appraisal						Current appraisal	
Factor	**TA565 Benralizumab**	**TA751 Dupilumab**	**TA431 Mepolizumab**	**TA671 Mepolizumab**	**TA278 Omalizumab**	**TA479 Reslizumab**	**Chosen values**	**Justification**
Treatment waning effect?	Not included	Not included	Not included	NA	NR	Not included	Not included	There is no evidence to suggest there is a loss of efficacy of tezepelumab over time. Consistent with previous NICE submissions
Source of clinical outcome data	SIROCCO, CALIMA, ZONDA	QUEST, VENTURE	MENSA	NICE TA431	INNOVATE (adults and adolescents) and IA-05 EUP (children)	Studies 3082 and 3082 Asthma-related mortality: Roberts 2013	NAVIGATOR and SOURCE	Consistent with reference case
Source of utilities	EQ-5D: pooled SIROCCO/CALIMA AQLQ: mapped from ZONDA	QUEST	SGRQ data from MENSA mapped to EQ-5D Utilities for exacerbations: Lloyd 2007	NICE TA431	AQLQ data from INNOVATE mapped to EQ-5D Exacerbations: Lloyd 2007	AQLQ data from 3082 and 3083 mapped to EQ-5D Exacerbations: Lloyd 2007 Controlled/uncontrolled asthma: Willson 2014	Mixed regression model of EQ-5D from NAVIGATOR, SOURCE, and Sullivan et al 2011 (161)	Consistent with reference case and with previous NICE submission TA565 (90)
Source of costs	NHS reference costs and PSSRU	NR in committee papers	Resource use: NHS reference costs, omalizumab HTA, and PSSRU Exacerbation costs: MENSA	NICE TA431	Resource use: trial data Unit costs: NHS reference costs and PSSRU	Resource use: NHS reference costs, omalizumab HTA, and clinical experts Health state costs: NHS reference costs, PSSRU, and Willson 2014	PSSRU, NHS reference costs, Willson 2014 (67)	Consistent with reference case and previous NICE submissions

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; HTA, health technology assessment; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PSSRU, Personal Social Services Research Unit.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention in the model was tezepelumab 210 mg SC Q4W in addition to SoC as used in the pivotal tezepelumab clinical trials described in Section B.2.3 and as per the NICE scope (see Table 2).

B.3.2.3.2 Comparators

Comparators included in the model were those listed in the NICE scope (Table 2), with the exception of reslizumab + SOC:

- Benralizumab + SoC
- Mepolizumab + SoC
- Omalizumab + SoC
- Dupilumab + SoC
- SoC alone

The NICE methods guide 2013 states that judgements on the appropriateness and relevance of comparator technologies will be based on established NHS practice in England, the natural history of the condition without suitable treatment, existing NICE guidance, cost effectiveness, and the licensing status of the comparator (160). Reslizumab + SoC was excluded as a comparator in economic modelling on the basis of it not representing established NHS practice in the target population. An analysis of patient records from the UK Severe Asthma Registry found that only 9 of 2,225 severe asthma patients (0.4%) were in receipt of reslizumab therapy, equating to a 0.6% share for biologic treated patients (73). No data are available for the target population of patients with 3 or more exacerbations in the prior year or those in receipt of mOCS, but AstraZeneca estimates reslizumab's share to be approximately 0.2% in these patients (please see budget impact submission). Whilst AstraZeneca fully expects tezepelumab + SoC to be cost-effective when compared with reslizumab + SoC, omitting it as a comparator negates the need for the inclusion of a further post-hoc subgroup in economic modelling, since the NICE recommended population for reslizumab (88) differs to (is a subset of) that for which both mepolizumab and benralizumab are recommended (90, 92).

Each comparator biologic was used in the model in line with its NICE-recommended patient population, as described in Table 97. Given the lack of head-to-head data for

tezepelumab versus comparator biologics, indirect treatment comparisons (described in Section B.2.9) were used to inform the model for the various patient subpopulations considered (outlined in Table 99).

Table 99: Patient populations and treatments included in the model

Population	Tezepelumab	Benralizumab	Dupilumab	Mepolizumab	Omalizumab	SoC
Anti-IL-5 eligible	✓	✓		✓		
Dupilumab eligible	✓		✓			
Omalizumab eligible	✓				✓	
Non-bio eligible (3+ exacs OR mOCS)	✓					✓

Abbreviations: exacs, exacerbations; IL, interleukin; mOCS, maintenance oral corticosteroid treatment; SoC, standard of care.

B.3.3 Clinical parameters and variables

B.3.3.1 Population baseline characteristics

Patient population baseline characteristics used in the model base case (Table 100) were sourced from Jackson 2021 (73), which reported demographic, clinical, and treatment characteristics for patients in the UK Severe Asthma Registry

The use of alternative baseline characteristics, sourced from the pivotal tezepelumab trials and from a previous NICE appraisal, was explored in scenario analysis (see Section B.3.8.4.2).

Table 100: Baseline patient characteristics

Parameter	Mean	SD/ (range)	Source	SE	Comment
Anti-IL-5 eligible					
Age (years)	50.7	14.1	Jackson 2021 (73)	0.421	
Percentage male (%)	39.0	NA		3.9†	
Percentage mOCS users (%)	65.0	NA		6.5†	
mOCS baseline dose (mg/day)	10	(8,18)		0.075‡	
Dupilumab eligible					
Age (years)	49.7	14.3	Jackson 2021 (73)	0.366	No dupilumab-specific data in Jackson 2021. Data for "Biologic therapy" population used as best proxy
Percentage male (%)	37.6	NA		3.8†	
Percentage mOCS users (%)	NA	NA		NA	

Parameter	Mean	SD/ (range)	Source	SE	Comment
mOCS baseline dose (mg/day)	NA	NA	NICE dupilumab guidance (94)	NA	Only dupilumab 200 mg dose is NICE-recommended for severe asthma. This dose is not licensed for mOCS patients
Omalizumab eligible					
Age (years)	47.6	14.6	Jackson 2021 (73)	0.805	
Percentage male (%)	33.1	NA		3.3	
Percentage mOCS users (%)	44.6	NA		4.5	
mOCS baseline dose (mg/day)	10	(5,15)		0.138‡	
Non-bio eligible (3+ exacerbations OR mOCS)					
Age (years)	49.1	14.3	Jackson 2021 (73)	0.546	No data specific to this population in Jackson 2021. Data for "No biologic therapy" population used as best proxy
Percentage male (%)	37.7	NA		3.8	
Percentage mOCS users (%)	33.5	NA		3.4	
mOCS baseline dose (mg/day)	6	(0,15)		0.143‡	

Abbreviations: IL, interleukin; mOCS: maintenance oral corticosteroid treatment; NA, not applicable; NICE, National Institute for Health and Care Excellence; SD, standard deviation; SE: standard error.
† Assumed to be 10% of the mean.
‡ SE was calculated from an estimate for SD, where SD was assumed to equal one quarter of the range.

B.3.3.2 Treatment efficacy

Treatment efficacy was captured in the model through cost offsets and QALY gains. The main treatment benefits associated with tezepelumab versus SoC were as follows:

- Reduction in the rate of exacerbations (defined as an exacerbation requiring either an mOCS burst, an A&E visit, or hospitalisation)
  - Costs offsets through the avoidance of additional healthcare expenditure due to an exacerbation
  - QALY gains through the reduction in utility decrements associated with experiencing an exacerbation
- Reduction in the proportion of exacerbations leading to hospitalisation
  - Additional cost offsets through the avoidance of hospitalisation due to an exacerbation event
  - Additional QALY gains through the avoidance of utility decrements associated with being hospitalised
- Reduction in ACQ-6 score

  - Cost offsets in the reduction of resource use associated with patients staying in a controlled asthma state for longer
  - QALY gains associated with higher health-related quality of life in a controlled asthma state
- OCS sparing
  - Cost offsets and QALY gains through the reduction of mOCS dose and avoidance of OCS-related adverse events

B.3.3.2.1 Trial data

Transitions

In the base case, patients could transition between non-fatal health states of controlled asthma, uncontrolled asthma, controlled exacerbation, and uncontrolled exacerbation. The probability of transition between health states was adjusted for mortality to allow for patients to die of asthma-related or exacerbation-related reasons (in addition to background mortality).

The model included four different sets of transition matrices for tezepelumab for each population, categorised as follows:

- Pre-assessment response with mOCS
- Pre-assessment response without mOCS
- Post-assessment response with mOCS
- Post-assessment response without mOCS

The model also included two sets of transition matrices for SoC which were assumed to remain constant over the model time horizon:

- Pre-assessment response with mOCS
- Pre-assessment response without mOCS

The four sets of transition matrices were reflective of the changing efficacy of patients pre- and post-response assessment and the adjusted efficacy of patients in receipt of mOCS. The inclusion of these transition matrices allowed for the model to fully capture the benefit of tezepelumab in reducing the need for mOCS in patients versus SoC.

For SoC, no response was assessed and therefore patient transition matrices were only stratified by whether they were in receipt of mOCS or not. Given that patients would discontinue onto SoC or remain on a biologic, and there was a further categorisation

based on mOCS use (with or without mOCS), it was important that the redistribution of mOCS users was reflected within the transition probabilities used in the model.

Transition probabilities were derived from NAVIGATOR and SOURCE trial data using 4-weekly count data assuming last observation carried forward, i.e. patients were assumed to remain in a health state until an observation indicating that they had moved. All count data across the entire follow-up of the trial were summed to generate a count data transition matrix which was converted into probabilities by taking the proportions of counts across each row in the transition matrix. ACQ-6 scores, as described in Table 1 (Glossary), were used to inform the transition from controlled asthma to uncontrolled asthma. SEs were derived assuming a normal distribution and using the formula:

$$SE_{transition} = \sqrt{\frac{p(1-p)}{N}}$$

where p was the probability of transitioning and N was the total number of observations in that row. 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.

Transition matrices for each population considered in the model are presented in Table 101 to Table 104 below.

Table 101: Transition probabilities (Anti-IL-5 eligible)

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

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

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

Table 102: Transition probabilities (Dupilumab 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: 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 103: Transition probabilities (Omalizumab eligible)

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

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

Abbreviations: 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 104: Transition probabilities (Non-bio eligible [3+ exacerbations OR mOCS])

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

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

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

Abbreviations: mOCS, maintenance oral corticosteroid treatment; 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.

Exacerbation distributions

Three types of exacerbation were included in the model:

- OCS burst: Use of systemic corticosteroids (or a temporary increase in a stable mOCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids, with no hospitalisation
- A&E visit: An urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as above) with no hospitalisation
- Hospitalisation: 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.

When patients experienced an exacerbation, the form that the exacerbation took was determined by a defined proportion. In the base case, the exacerbation distributions were partitioned by the exacerbation type (i.e. controlled or uncontrolled) and by whether the patients were in receipt of mOCS (Table 105 to Table 108). The exacerbation distributions for tezepelumab and SoC were informed directly from NAVIGATOR and SOURCE. As for the derivation of transition state probabilities, count data from the trials were used to determine the proportions. The total numbers of exacerbation events were summed over the follow-up of the trial and the proportions attributed to an mOCS burst, A&E visit, and hospitalisation were determined. The calculations for the SE were the same as for the transition probabilities.

Table 105: Exacerbation distributions (Anti-IL-5 eligible)

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

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

Abbreviations: A&E, Accident and Emergency; IL, interleukin; OCS, oral corticosteroid; SE, standard error; SoC, standard of care.

Table 106: Exacerbation distributions (dupilumab eligible)

		Exacerbation distribution					
		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; NA, not applicable; OCS, oral corticosteroid; SE, standard error; SoC, standard of care.
† Dupilumab is not recommended by NICE in patients on mOCS.

Table 107: Exacerbation distributions (omalizumab eligible)

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

Abbreviations: A&E, Accident and Emergency; OCS, oral corticosteroid; SE, standard error; SoC, standard of care.

Table 108: Exacerbation distributions (non-bio eligible [3+ exacs OR mOCS])

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

		Exacerbation distribution					
		With OCS			Without OCS		
		Mean	SE	Source	Mean	SE	Source
	OCS burst	[redacted]	[redacted]	SOURCE	[redacted]	[redacted]	NAVIGATOR
	A&E visit	[redacted]	[redacted]		[redacted]	[redacted]	
	Hospitalisation	[redacted]	[redacted]		[redacted]	[redacted]	

Abbreviations: A&E, Accident and Emergency; exacs, exacerbations; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SE, standard error; SoC, standard of care.

Duration of exacerbations

Utility decrement associated with an exacerbation was assumed to apply for 4 weeks, in line with the approach taken in previous NICE appraisals.

OCS sparing

Another treatment effect of tezepelumab is reduced requirement for mOCS. The model captured the benefits of mOCS reduction through reduced adverse events associated with mOCS, and reduced treatment costs. To capture this treatment effect, the model initially defined the proportion of patients using mOCS at baseline and applied a reduction at a user-defined mOCS sparing week (52 weeks in the base case). The reduction in mOCS was stratified into categories as follows:

- No reduction
- >0% to <50% reduction
- 50% to <75% reduction
- 75% to <90% reduction
- 90% to <100% (assumed to be discontinuation)

At the time of mOCS sparing, the model assumed that the proportion of patients with a 90% to 100% reduction in mOCS would discontinue mOCS altogether. Patients who discontinued mOCS proceeded to receive the efficacy profile of patients without mOCS leading to a reduction in exacerbation rates (see Table 101 for the probabilities of exacerbations). For patients who did not discontinue, but had their mOCS dose reduced, the magnitude of the reduction was determined by the user. As the reduction parameter was categorical whereas the mOCS dose was continuous, there was uncertainty as to where, within each range, the true percent reduction in mOCS lay. Therefore, the magnitude was determined via a scaling system that either took the lower bound, the median, or the upper bound of the categorical reduction. Table 109 presents the

magnitude of reduction according to whether the dose reduction was low, medium, or high. In the base case, a medium reduction was applied as a conservative assumption.

Table 109: mOCS dose reduction magnitudes (all populations)

Dose reduction category	Dose reduction applied (%)		
	Low	Medium (base case)	High
No reduction	0.0	0.0	0.0
>0% to 50%	0.0	25.0	50.0
50% to 75%	50.0	62.5	75.0
75% to <90%	75.0	82.5	90.0
90% to 100%	90.0	95.0	100.0

Abbreviations: mOCS, maintenance oral corticosteroid treatment.

Data informing the reduction in mOCS were derived from the SOURCE trial. Data from SOURCE trial recorded the categorical reduction in mOCS from baseline versus the 52-week mOCS sparing timing. In order to derive the proportions, count data were used to determine the proportions of patients experiencing each reduction in mOCS. The SE were derived using the same approach as for the transition probabilities.

The percentages of patients experiencing a reduction in mOCS, by patient population considered in the model, are presented in Table 110 to Table 112. As dupilumab is not recommended by NICE in patients on mOCS, it was not necessary to consider this for the dupilumab eligible population. As described above, the proportion of patients who had a 90% to 100% reduction in mOCS (0.541 for tezepelumab and 0.461 for SoC) were assumed to discontinue mOCS altogether.

Table 110: mOCS dose reduction magnitudes (Anti-IL-5 eligible)

Dose reduction category	Dose reduction probability applied		Source
	Mean	SE	
Tezepelumab			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	
SoC			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	

Dose reduction category	Dose reduction probability applied		Source
	Mean	SE	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	

Abbreviations: IL, interleukin; mOCS, maintenance oral corticosteroid treatment; SE, standard error; SoC, standard of care.

Table 111: mOCS dose reduction magnitudes (omalizumab eligible)

Dose reduction category	Dose reduction probability applied		Source
	Mean	SE	
Tezepelumab			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	
SoC			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	

Abbreviations: mOCS, maintenance oral corticosteroid treatment; SE, standard error; SoC, standard of care.

Table 112: mOCS dose reduction magnitudes (non-bio eligible [3+ exacs OR mOCS])

Dose reduction category	Dose reduction probability applied		Source
	Mean	SE	
Tezepelumab			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	
SoC			
No reduction	[redacted]	[redacted]	SOURCE
>0% to 50%	[redacted]	[redacted]	
50% to 75%	[redacted]	[redacted]	
75% to <90%	[redacted]	[redacted]	
90% to <100%	[redacted]	[redacted]	

Abbreviations: exacs, exacerbations; mOCS, maintenance oral corticosteroid treatment; SE, standard error; SoC, standard of care.

Discontinuation

The model considered two types of treatment discontinuation:

- Discontinuation resulting from natural attrition
- Discontinuation following response assessment (treatment discontinuation due to a lack of response)

Patients were subject to natural attrition with tezepelumab treatment over the course of the model. Once they had discontinued, they were assigned the same efficacy profile as patients receiving SoC. The response assessment in the model was a single timepoint where, in clinical practice, clinicians would determine whether patients continued using a biologic based on their response to treatment prior to the response week. Treatment discontinuation parameters were not applied to the SoC arm of the model as patients could not discontinue from SoC.

The natural attrition rate of tezepelumab was derived from NAVIGATOR and SOURCE trial data. The number of patients discontinuing tezepelumab as a ratio of the time they were exposed to tezepelumab was used to derive a rate and scaled to 4 weeks in accordance with the cycle length of the model. For discontinuation following response assessment, the proportion of patients who achieved the criteria for response out of the entire cohort was used to determine the probability of achieving response. The complement of this was then used in the model to inform the probability of discontinuation.

Patients were considered responders based on the primary efficacy endpoint of the NAVIGATOR trial: exacerbation rate reduction. Due to limited data beyond 52 weeks, transition probabilities for responders were based on the initial 52 weeks of data for this responder population (i.e. the assumption was made that in years subsequent to the first year, exacerbations and asthma control status would align with that of Year 1). Due to mOCS dose reduction in SOURCE, it was not considered appropriate to use exacerbation rate reduction endpoint data from this trial to inform discontinuation probability. Probability of discontinuation with mOCS was therefore assumed to be equal to that of without mOCS.

The inputs relating to discontinuation, by patient population considered in the model, are presented in Table 113 (natural discontinuation) and Table 114 (response assessment).

The same discontinuation probabilities assigned to tezepelumab were also applied to the comparator biologics.

Table 113: Tezepelumab discontinuation probability: Natural discontinuation (4-weekly rate)

With mOCS			Without mOCS		
Mean rate	**SE**	**Source**	**Mean rate**	**SE**	**Source**
[redacted]	[redacted]	NAVIGATOR+SOURCE	[redacted]	[redacted]	NAVIGATOR

Abbreviations: mOCS, maintenance oral corticosteroid treatment; SE, standard error.

Table 114: 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**
Anti-IL-5 eligible	[redacted]	[redacted]	Assumed equal to without mOCS†	[redacted]	[redacted]	NAVIGATOR
Dupilumab eligible	[redacted]	[redacted]		[redacted]	[redacted]	
Omalizumab eligible	[redacted]	[redacted]		[redacted]	[redacted]	
Non-bio eligible (3+ exacs OR mOCS)	[redacted]	[redacted]		[redacted]	[redacted]	

Abbreviations: exacs, exacerbations; IL, interleukin; mOCS, maintenance oral corticosteroid treatment; SE, standard error.
† Due to mOCS dose reduction in SOURCE, it was not considered appropriate to use exacerbation rate reduction endpoint data from this trial to inform discontinuation probability. Probability of discontinuation with mOCS was therefore assumed to be equal to that of without mOCS.

B.3.3.2.2 NMA data

Transitions

To incorporate indirect comparison to biologics not included in the tezepelumab trials, relative annual exacerbation rates were applied versus tezepelumab to inform transition probabilities. For the base case, these values were derived from the NMA described in Section B.2.9.

To appropriately apply NMA-derived relative effects, the 4-weekly transition probabilities for tezepelumab were converted to annual rates, the relative exacerbation rates applied and subsequently converted back to 4-weekly probabilities to be applied in the model. In the base case, it was assumed that transition probabilities between controlled and uncontrolled asthma were equivalent between all biologic therapies. Since the NMA did not distinguish between patients on mOCS or not, or whether they were responders or not, the same relative treatment effect was applied in the model irrespective of mOCS and responder status.

Since NMA data were available for the ITT population and several subgroups, it was necessary to choose the most appropriate data to inform the base case. In selecting, consideration was given to alignment of the population in which the NMA was derived and the population of interest and to the availability of NMA data across endpoints used on the model.

For benralizumab + SoC and mepolizumab + SoC, the population of interest (anti-IL-5 eligible) has high eosinophil count and ≥3 exacerbations (or on mOCS). The NMA did not distinguish between patients on mOCS and not, so the NMA data most closely aligned to the population of interest was that relating to the EOS High: ≥300 cells/μL and ≥3 Exacs in last 12 months subgroups. For the former subgroup, data were available to inform four of the five model endpoints that required NMA data (all endpoints except relative annual hospitalisation rate), whereas for the latter it was available for one endpoint only – relative annual exacerbation rate. On this basis, NMA data for the EOS High: ≥300 cells/μL subgroup were chosen for the base case for all endpoints except relative annual hospitalisation rate. No NMA subgroup data were available for relative annual hospitalisation rate, so ITT NMA data were used for base case. Sensitivity analysis was performed, substituting ≥3 Exacs in last 12 months subgroup NMA data (only available for comparison vs benralizumab + Soc) for EOS High: ≥300 cells/μL subgroup data, for the relative annual exacerbation rate endpoint.

For dupilumab + SoC, the population of interest (dupilumab eligible), reflects patients with eosinophil count is ≥150 cells/μL and 4+ exacerbations in the prior year and high FeNO count, who are not eligible for other biologics. 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. On this basis, for the relative annual exacerbation rate endpoint, NMA data relating to the EOS Low: <300 cells/μL subgroup were chosen for the base case. The only data available to inform the relative annual hospitalisation rate and mOCS sparing endpoints were ITT NMA data, so this was used for the base case. Sensitivity analyses were performed for the relative annual exacerbation rate endpoint, using firstly FeNO High: ≥25 ppb subgroup data, then ≥3 Exacs in last 12 months subgroup NMA data and finally EOS High: ≥150 cells/μL subgroup data (Section B.3.8.4.4).

For omalizumab + SoC, the population of interest (omalizumab eligible) reflects patients with allergic asthma and 4+ exacerbations in the prior year (or on mOCS). Accordingly,

NMA data for the allergic subgroup were used to inform the base case for the relative annual exacerbation rate endpoint. Only ITT NMA data were available for relative annual hospitalisation rate. No NMA data were available to inform mOCS sparing endpoints, so equivalence was assumed between omalizumab + SoC and tezepelumab + SoC.

Relative annual exacerbation rates used in the model for each patient population considered are presented in Table 115 to Table 117.

Table 115: Relative annual exacerbation rate (anti-IL-5 eligible)

Intervention	Relative annual exacerbation rates vs tezepelumab + SoC		
	Mean	Log (SE)	Source
Benralizumab + SoC	1.59	0.29	High blood EOS level (≥300 cells/μL) subgroup NMA (Section B.2.9.2.1.2)
Mepolizumab + SoC	1.22	0.32	

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

Table 116: Relative annual exacerbation rate (dupilumab eligible)

Intervention	Relative annual exacerbation rates vs tezepelumab + SoC		
	Mean	Log (SE)	Source
Dupilumab + SoC	1.64	0.85	Low blood EOS level (<300 cells/μL) subgroup NMA (Section B.2.9.2.1.4)

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

Table 117: Relative annual exacerbation rate (omalizumab eligible)

Intervention	Relative annual exacerbation rates vs tezepelumab + SoC		
	Mean	Log (SE)	Source
Omalizumab + SoC	1.64	0.40	Allergic asthma subgroup NMA (Section B.2.9.2.1.8)

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

Exacerbation distributions

To incorporate the relative effects of tezepelumab in reducing the rate of hospitalised exacerbation, the relative rate of hospitalised exacerbation from NMA data were applied. Similar to the application of the relative rate of exacerbations, the proportion of hospitalisations for tezepelumab was converted to an annual rate, and the relative effect applied and converted back to a 4-weekly probability to be applied in the model. An element of double counting occurred when applying the ITC in this fashion, with the relative effects of exacerbations and hospitalisations being applied simultaneously, albeit

hospitalised exacerbations make up a very low proportion of all exacerbations, so the impact is small.

The relative annual hospitalised exacerbation rates are presented in Table 118. Since the NMA did not distinguish between patients on mOCS or not, or whether they were responders or not, the same relative treatment effect was applied in the model irrespective of mOCS and responder status.

Table 118: Relative annual hospitalised exacerbation rates (all populations)

Intervention	Relative annual hospitalised exacerbation rates (vs tezepelumab + SoC)		
	Mean	Log (SE)	Source
Benralizumab + SoC	2.86	0.68	Reduction in AAER leading to hospitalisations NMA (Section B.2.9.2.2)
Dupilumab + SoC	2.78	0.80	
Mepolizumab + SoC	1.85	0.70	
Omalizumab + SoC	2.50	0.70	
Reslizumab + SoC	3.45	0.70	

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

Duration of exacerbations

No NMA data were available to inform the relative effect of tezepelumab versus the comparator biologics in reducing the duration of exacerbations. Exacerbation durations for each comparator were therefore assumed to last for 4 weeks (one cycle), consistent with previous NICE appraisals.

OCS sparing

The model incorporated NMA data informing the OR of reduction in mOCS. The model used the probability of a reduction in mOCS for tezepelumab, converted this to an OR, applied the OR, then converted this back to a probability to inform the reduction in mOCS for the biologic. Similar to the assumption made for tezepelumab and SoC, in which the 90% to 100% category was assumed to be the probability of discontinuing mOCS, the OR for the ≥90% reduction in mOCS was used to inform the relative effect of discontinuing mOCS. As the NMA did not report on <50% mOCS reductions, it was assumed that after application of the relative effects for the ≥50% reductions, an equally-weighted distribution of proportions to tezepelumab were applied for the proportion with no reduction and proportion with a 0% to 50% reduction.

The ORs reported in the NMA and applied in the model for each patient population considered are presented in Table 119 to Table 120. (The OR for mOCS reduction in the

non-bio eligible [3+ exacs OR mOCS] population were sourced directly from the SOURCE trial) The NMA did not identify/include any suitable studies for omalizumab. The model therefore assumed equivalent efficacy to tezepelumab (an OR of 1 was applied), as explained further in Table 138.

In the modelled patient populations, subgroup analyses from the NMA were applied. The ability to derive these was limited by the available published data for comparator biologics and assumptions were required, as described in the Transitions subsection of Section B.3.3.2.2).

As dupilumab is not recommended by NICE in patients on mOCS, it was not necessary to consider dupilumab for odds of mOCS reduction.

Table 119: OR for mOCS reduction (anti-IL-5 eligible)

Reduction scale	Intervention (+ SoC)	OR for reduction in mOCS vs tezepelumab + SoC		
		Mean	Log (SE)	Source
≥50%	Benralizumab	[redacted]	[redacted]	High blood EOS level (≥300 cells/µL) subgroup NMA (Section B.2.9.2.3)
	Mepolizumab	[redacted]	[redacted]	
≥75%	Benralizumab	[redacted]	[redacted]	
	Mepolizumab	[redacted]	[redacted]	
≥90%	Benralizumab	[redacted]	[redacted]	
	Mepolizumab	[redacted]	[redacted]	

Abbreviations: EOS, eosinophil; IL, interleukin; mOCS, maintenance oral corticosteroid treatment; NMA, network meta-analysis; OR, odds ratio; SE, standard error; SoC, standard of care.

Table 120: OR for mOCS reduction (omalizumab eligible)

Reduction scale	Intervention (+ SoC)	OR for reduction in mOCS vs tezepelumab + SoC		
		Mean	Log (SE)	Source
≥50%	Omalizumab	[redacted]	[redacted]	Assumption
≥75%	Omalizumab	[redacted]	[redacted]	Assumption
≥90%	Omalizumab	[redacted]	[redacted]	Assumption

Abbreviations: mOCS, maintenance oral corticosteroid treatment; OR, odds ratio; SE, standard error; SoC, standard of care.

Discontinuation

No indirect evidence for the relative effects of tezepelumab versus the comparator biologics on response rates were available, so they were therefore assumed to be equivalent. The assumed natural rate of attrition and the probability of discontinuing

comparator biologic treatment at the assessment week were equal to those of tezepelumab, as presented in Table 113.

B.3.3.3 Consequences of mOCS use

OCS-related adverse events were modelled in terms of their impact on both costs and QoL. In order to apply these costs and QoL decrements, as well as the effects of mOCS sparing, the frequency of adverse events based on mOCS dose were included in the model.

In order to quantify the impact of mOCS use, and as previously used in the benralizumab NICE appraisal TA565 (90), AstraZeneca commissioned a matched historical cohort study using the Optimum Patient Care Research Database (OPCRD), and the Clinical Practice Research Datalink (CPRD) database (AstraZeneca data on file 2017). The study consisted of a minimum 1-year baseline period and a minimum 2 years' outcome period, on either side of an index date. The index date was the date of the first recorded prescription for a parenteral or oral corticosteroid for patients in the mOCS arm, while that for the non mOCS arm was the nearest primary care visit to the matched-case index date.

Modelled adverse events associated with mOCS use and their annual probabilities are summarised in Table 121. Annual probabilities were converted to 4-week probabilities in the model.

Table 121: mOCS adverse event frequency by dose (annual probabilities)

Adverse event	OCS dose	Annual probabilities by mOCS dose (mg/day)		Source
		Mean	SE	
Type 2 diabetes mellitus	0 to <0.5	0.006	0.001	AZ data on file 2017
	0.5 to <2.5	0.014	0.001	
	2.5 to <5	0.020	0.002	
	5 to <7.5	0.025	0.002	
	7.5 to <15	0.042	0.004	
	>15	0.080	0.008	
Osteoporosis	0 to< 0.5	0.002	0.000	
	0.5 to <2.5	0.007	0.001	
	2.5 to <5	0.015	0.002	
	5 to <7.5	0.020	0.002	
	7.5 to <15	0.033	0.003	
	>15	0.012	0.001	

Adverse event	OCS dose	Annual probabilities by mOCS dose (mg/day)		Source
		Mean	SE	
Glaucoma	0 to <0.5	0.001	0.000	
	0.5 to <2.5	0.003	0.000	
	2.5 to <5	0.004	0.000	
	5 to <7.5	0.008	0.001	
	7.5 to <15	0.005	0.000	
	>15	0.010	0.001	
Cataract	0 to <0.5	0.005	0.001	
	0.5 to <2.5	0.012	0.001	
	2.5 to <5	0.023	0.002	
	5 to <7.5	0.026	0.003	
	7.5 to <15	0.032	0.003	
	>15	0.037	0.004	
Myocardial infarction	0 to <0.5	0.002	0.000	
	0.5 to <2.5	0.004	0.000	
	2.5 to <5	0.009	0.001	
	5 to <7.5	0.011	0.001	
	7.5 to <15	0.013	0.001	
	>15	0.010	0.001	
Heart failure	0 to <0.5	0.002	0.000	
	0.5 to <2.5	0.006	0.001	
	2.5 to <5	0.013	0.001	
	5 to <7.5	0.020	0.002	
	7.5 to <15	0.021	0.002	
	>15	0.034	0.003	
Cerebrovascular accident	0 to <0.5	0.002	0.000	
	0.5 to <2.5	0.006	0.001	
	2.5 to <5	0.008	0.001	
	5 to <7.5	0.010	0.001	
	7.5 to <15	0.008	0.001	
	>15	0.006	0.001	
Renal impairment	0 to <0.5	0.011	0.001	
	0.5 to <2.5	0.027	0.003	
	2.5 to <5	0.044	0.004	
	5 to <7.5	0.048	0.005	
	7.5 to <15	0.072	0.007	
	>15	0.108	0.011	

Adverse event	OCS dose	Annual probabilities by mOCS dose (mg/day)		Source
		Mean	SE	
Peptic ulcer	0 to <0.5	0.001	0.000	
	0.5 to <2.5	0.002	0.000	
	2.5 to <5	0.002	0.000	
	5 to <7.5	0.002	0.000	
	7.5 to <15	0.003	0.000	
	>15	0.011	0.001	
Pneumonia	0 to <0.5	0.003	0.000	
	0.5 to <2.5	0.008	0.001	
	2.5 to <5	0.016	0.002	
	5 to <7.5	0.020	0.002	
	7.5 to <15	0.030	0.003	
	>15	0.046	0.005	

Abbreviations: mOCS, maintenance oral corticosteroid treatment; SE, standard error

B.3.3.4 Mortality

B.3.3.4.1 Life tables and asthma

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 (see Section B.3.3.4.2). 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 (162). In order to avoid any double counting of mortality, asthma-specific mortality was subtracted from all-cause mortality to leave a resultant non-asthma-related mortality used to capture mortality not related to asthma.

The mortality data used in the model base case are presented in Appendix O.

B.3.3.4.2 Exacerbation-specific mortality

In England and Wales, deaths resulting from asthma are increasing. A 2019 analysis of ONS data by Asthma UK revealed that more than 1,400 adults and children died from asthma attacks in 2018, an 8% increase since 2017 (25). 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 (25).

In the model, exacerbation-specific mortality used input values from three UK studies: Watson 2007 (45), Roberts 2013 (46), and the 2014 National Review of Asthma Deaths (NRAD) report (163).

The methods used in the model for calculating mortality aligned with those described in the NICE submission for benralizumab (90) but with exacerbation data derived from NAVIGATOR and SOURCE. The approach assumed that asthma-related mortality could only occur following an exacerbation.

The Watson 2007 study reported mortality incidence over a period of 5 years, stratified by age, in an acute severe asthma population following a hospital admission (45). The data presented in Table 122 were derived from the reported deaths post 100,000 asthma admissions, with the associated SE derived from the reported 95% CI. For exacerbations resulting in an mOCS burst and an A&E visit, the data were combined with the results from the NRAD report (163)

Table 122: Probability of death following asthma-related hospital admission as reported in Watson 2007

Age band	Probability of death	
	Mean (95% CI)	Derived SE
17-44	0.003830 (0.002670,0.005290)	0.000668
45+	0.024780 (0.021290,0.028650)	0.001878
SE was derived using the formula $SE = \frac{CI_{upper} - CI_{lower}}{2 \times z_{1-\frac{\alpha}{2}}}$		

Abbreviations: CI, confidence interval; SE, standard error.
Source: Watson 2007 (45).

The NRAD report presented the locations of asthma-related deaths following exacerbations, summarised in Table 123. Deaths that were reported in patients' home addresses, nursing or residential homes, holidays or other sources were assumed attributable to an exacerbation treated via an mOCS burst, with the remaining locations assumed to be attributed to exacerbations treated via A&E visits and hospitalisations.

Table 123: Locations of asthma-related deaths reported in the NRAD report

Location of death	Exacerbation type	Reported deaths	
		N	Proportion
Home (private address)	OCS burst	80	0.467
Nursing/residential home		5	
Holiday		4	

Location of death	Exacerbation type	Reported deaths	
		N	Proportion
Other		2	
Hospital, pre-hospital arrest	A&E Visit	45	0.231
Hospital, arrest in hospital	Hospitalisation	59	0.303

Abbreviations: A&E: Accident and Emergency; NRAD, National Review of Asthma Deaths; OCS, oral corticosteroid; Source: NRAD report (163).

To derive the probability of death following an mOCS burst and A&E visit, the model assumed that the proportion of deaths following a hospitalised exacerbation was equivalent to the proportion of deaths following a non-hospitalised exacerbation. This was derived using the following formula:

$$p_{death\ from\ OCS\ burst} \times \frac{\%_{exacerbatio\quad from\ OCS}}{\%_{deaths\ from\ OCS}} = p_{death\ from\ hospitali} \times \frac{\%_{exacerbations\ from\ hospitalisatio}}{\%_{death\quad from\ hospitalisation}}$$

The parameters in the formula were summarised as follows:

- Probability of death from an mOCS burst was the estimable parameter
- % exacerbations from mOCS were the proportion of total exacerbations resulting in an mOCS burst (sourced from NAVIGATOR and SOURCE)
- % deaths from mOCS were the proportions of deaths following an mOCS burst (sourced from the NRAD report (163))
- Probability of death from hospitalised exacerbation was sourced from Watson 2007 (45)
- % exacerbations from hospitalisation were the proportion of total exacerbations resulting in a hospitalisation (sourced from NAVIGATOR and SOURCE)
- % deaths from hospitalisation were the proportions of deaths following a hospitalised exacerbation (sourced from the NRAD report (163))

Using the formula above, rearranging in order to get the probability of death following an mOCS burst yielded the following:

$$p_{death\ from\ OCS\ burst} = p_{death\ from\ hospitalisation} \times \frac{\%_{exacerbations\ from\ hospitalisation}}{\%_{death\ \ from\ hospitalisation}} \times \frac{\%_{deat\ \ \ from\ OCS}}{\%_{exacerbations\ from\ OCS}}$$

The distribution of total exacerbations as observed in the NAVIGATOR and SOURCE trials are presented in Table 124.

Table 124: Proportions of exacerbation types observed in NAVIGATOR and SOURCE

Exacerbation type	Proportion	Source
OCS burst	0.885	NAVIGATOR + SOURCE
A&E visit	0.043	
Hospitalisation	0.072	

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

As a representative example of deriving the probability of death following an mOCS burst for 17–44-year-olds, the formula worked as follows:

$$p_{deat\ \ \ from\ OCS\ burst} = 0.003830 \times \frac{0.072}{0.303} \times \frac{0.467}{0.885} = 0.000481$$

To derive standard errors for the mortality probabilities, the derived standard error from Watson 2007 (45) was passed through the same formula. The mortality probabilities are presented in Table 125.

Table 125: Probabilities of asthma-related death following an mOCS burst and A&E visit

Exacerbation type	Age band	Probability (SE)
OCS burst	17–44	0.000481 (0.000084)
	45+	0.003115 (0.000236)
A&E visit	17–44	0.004930 (0.000860)
	45+	0.031894 (0.002417)

Abbreviations: A&E, Accident and Emergency; mOCS, maintenance oral corticosteroid treatment; SE, standard error.

To determine the probability of death following hospitalised exacerbation, a 2013 study by Roberts et al (46) provided the most granular representation of mortality for hospital-admitted patients. Using a reported crude case-fatality of 0.9% (n=1,000) alongside odds ratios, the number of deaths during hospital admission allowed the calculation of hospital-related probabilities of death, as presented in Table 126.

Table 126: Probability of death following hospital admission

Age band	Number of deaths	Number of admissions	Probability of death
18–24	25	17,173	0.001456
25–34	30	20,785	0.001443
35–44	41	20,390	0.002011
45–54	89	19,856	0.004482
55–64	210	16,474	0.012747
65–100	605	21,779	0.027779

To best reflect an acute severe asthma population, relative rate ratios of the probabilities for the age bands over 45 were applied to the over 45 age band enrolled in the Watson 2007 study (45), as presented in Table 122. The adjustment assumed that total admissions were equally spread between the three age categories in order to provide age-stratified probabilities of death following asthma-related hospitalisation. The set of probabilities arrived at are presented in Table 127.

Table 127: Adjusted probabilities of death following hospitalisation

Age band	Unadjusted probability of death	Relative rate ratio	Deaths using relative rate ratios	Hospital admissions	Adjusted probability of death
45–54	0.004482	1.0	18	2,381	0.007560
55–64	0.012747	2.8	51	2,381	0.021420
65–100	0.027779	6.2	108	2,381	0.045360

A summary of the final set of mortality probabilities applied in the model are presented in Table 128 (Note that alternative values were explored in sensitivity analysis).

Table 128: Summary of mortality probabilities

Age band	Mean	SE[†]
OCS burst		
Patients aged 18–44	[redacted]	[redacted]
Patients aged 45+	[redacted]	[redacted]
A&E visit		
Patients aged 18–44	[redacted]	[redacted]
Patients aged 45+	[redacted]	[redacted]
Hospitalisation		
Patients aged 18–24	[redacted]	[redacted]
Patients aged 25–34	[redacted]	[redacted]

Age band	Mean	SE†
Patients aged 35–44	[redacted]	[redacted]
Patients aged 45–54	[redacted]	[redacted]
Patients aged 55–64	[redacted]	[redacted]
Patients aged 65+	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; OCS, oral corticosteroid; SE, standard error.
† Standard errors for hospitalisation-related probabilities were assumed to be 10% of the mean value.
Source: TA565 (90).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Mixed regression model

The model estimated utility using a mixed regression model. Patient characteristics were used to inform covariates in order to estimate utility in each cycle of the model. A mixed model approach was taken because it offered a number of advantages over simple summary measures or simple regression analytic techniques (e.g. general linear model [GLM]). Notably, the primary advantage of the mixed model approach was that it took into account the repeated measures structure of the trial data since it does not assume independence between observations. The mixed model approach also provided a flexible analytic framework, which accounts for additional complexities in the data using variations in the mixed modelling approach.

The mixed regression model, which included covariates for treatment with tezepelumab, ACQ score, and exacerbations were associated with significant differences in quality of life (Table 129). The mixed regression model indicated that the utility of an untreated patient without an exacerbation event and with controlled asthma would be [redacted]. The model also indicated that uncontrolled asthma was associated with a utility loss of [redacted]. Patients with an exacerbation event also incurred a loss in utility of [redacted] for an mOCS burst, [redacted] for an A&E visit, and [redacted] for hospitalised exacerbation. Additionally, the mixed regression model indicated that there was evidence that tezepelumab treatment was associated with a utility gain of [redacted] independent of differences in HRQoL captured by ACQ score and exacerbation (Table 129).

It was assumed that the effect of treatment with each comparator biologic was equivalent to that seen with tezepelumab.

Table 129: Mixed regression model for utility

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

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

B.3.4.2 Adverse reactions

As described in Section B.2.10.3, the evaluations of safety data submitted as part of the marketing authorisation application for tezepelumab were based on the primary safety pool which included 665 subjects who received tezepelumab 210 mg SC Q4W for up to 1 year, representing approximately 640 subject-years of exposure. Evaluation of AE data from the primary safety pool showed that:

- The overall incidence of subjects with AEs in the on-treatment period was similar between the tezepelumab and placebo arms (74.6 and 76.5% of subjects, respectively)
- The incidence of SAEs in the on-treatment period was 8.6% in tezepelumab-treated subjects and 13.0% in placebo-treated subjects
- There were no deaths in the tezepelumab arm. There were two deaths in the placebo arm
- The four most common AEs reported in the tezepelumab arm were nasopharyngitis (19.5%), upper respiratory tract infection (9.3%), headache (7.8%), and asthma (7.4%); in comparison, incidences of subjects with these AEs in the placebo arm were 19.1, 13.3, 7.5, and 15.7%, respectively

Because of the lack of difference in AE rates between subjects treated with tezepelumab and those who received placebo, treatment-specific AEs were excluded from the model.

B.3.4.3 OCS-related adverse event disutility

A fixed disutility value was applied for each OCS-related AE, as shown in Table 130. The disutilities used were the same as those used in the benralizumab NICE submission, TA565 (90), which were derived from a 2011 UK study by Sullivan et al (161). Values were

input as annual disutilities which were then converted to cyclical values to be applied in the model.

Table 130: EQ-5D disutility decrement by OCS-related AE

Adverse event	Mean	SE	Source
Type 2 diabetes mellitus	0.062	0.004	TA565 (90) Sullivan 2011 (161)
Osteoporosis	0.042	0.006	
Glaucoma	0.028	0.006	
Cataract	0.027	0.006	
Myocardial infarction	0.056	0.011	
Heart failure	0.103	0.016	
Cerebrovascular accident	0.101	0.012	
Renal impairment	0.096	0.012	
Peptic ulcer	0.055	0.014	
Pneumonia	0.079	0.042	

Abbreviations: AE, adverse event; EQ-5D, European Quality of Life-5 Dimensions; OCS, oral corticosteroid; SE, standard error.
Type 2 diabetes mellitus assumed to be disease code CCC049 – diabetes without complications.
Osteoporosis assumed to be disease code CCC206 – osteoporosis.
Glaucoma assumed to be disease code CCC088 – glaucoma.
Cataract assumed to be disease code CCC086 – cataract.
Myocardial infarction assumed to be disease code CCC100 – acute myocardial infarction.
Heart failure assumed to be disease code CCC108 – congestive heart failure.
Cerebrovascular accident assumed to be disease code CCC109 – acute cerebrovascular disease.
Renal impairment assumed to be disease code CCC161 – other diseases or kidney and ureters.
Peptic ulcer assumed to be disease code CCC139 – gastroduodenal ulcer.
Pneumonia assumed to be disease code CCC132 – lung diseases due to external agents.

B.3.4.4 Health-related quality-of-life studies

An SLR (initial search on 6th November 2017, updated search on 23rd November 2021) was conducted to identify studies reporting utility data relevant to the decision problem (i.e. studies reporting health state utility values in patients aged ≥12 years with severe asthma).

Full details of the SLR methodology and results are provided in Appendix H.

In total, across the original and updated SLR, 31 studies were identified as eligible for inclusion. Of these, ten were conducted in the UK. Overviews of the ten UK studies are provided in Table 131. A tabulated overview of the complete set of 31 included studies is provided in Appendix H.

Since utility data were available direct from the tezepelumab pivotal trials, these were used in the model, in line with the NICE reference case, in favour of the utility data identified by the SLR.

Table 131: Overview of the ten UK studies identified in the HRQoL SLR

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Briggs 2021 (159) UK, Denmark, Germany	Adult participants from the house dust mite (HDM) sublingual allergen immunotherapy (SLIT) trial – 834 participants	Budesonide and SABA, followed by SQ HDM SLIT-tablet or placebo	Patients reporting moderate or severe exacerbation, N=204 (number of severe exacerbation not reported)	EQ-5D-3L and AQL-5D	7 days following a severe exacerbation	EQ-5D-3L: 0.76 AQL-5D: 0.768
					14 days following a severe exacerbation	EQ-5D-3L: 0.791 AQL-5D: 0.809
					21 days following a severe exacerbation	EQ-5D-3L: 0.798 AQL-5D: 0.816
					28 days following a severe exacerbation	EQ-5D-3L: 0.808 AQL-5D: 0.832
Burn 2019 (164) UK	Patients from the UK severe asthma registry who received bronchial thermoplasty between 01/06/11 and 30/09/6 with follow up data available	Bronchial thermoplasty	Baseline N=42; 12-month follow-up N=29; 24-month follow up N=18	EQ-5D	Severe asthma at baseline	0.53 [0.38]
					Severe asthma at 12-months follow-up	0.62 [0.38]
					Severe asthma at 24-months follow-up	0.65 [0.35]
Hyland 2021 (165) UK	Patients with severe asthma (GINA step 4 & 5) commencing a biologic treatment in normal clinical care following NICE guidelines	Omalizumab, mepolizumab, benralizumab, reslizumab	Intention to treat (ITT) group – baseline N=103, 16 weeks N=41; per protocol (PP) group – N=22	EQ-5D	Severe asthma (baseline, ITT)	0.69 [0.23]
					Severe asthma (baseline, PP)	0.71 [0.19]
					Severe asthma (16 weeks, ITT)	0.76 [0.21]
					Severe asthma (16 weeks, PP)	0.8 [0.18]
Lloyd 2007 (166) UK	Patients with a diagnosis of moderate or severe asthma (BTS level 4 or 5) [conducted at four	Patients included were managed with: ≥ 1 high dose ICS combined with any oral or inhaled	N=112	EQ-5D (version not reported) [collected within four weeks of a severe	No exacerbation	0.89 [0.15]
					Exacerbation requiring mOCS (moderate exacerbation)	0.57 [0.36)

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
	specialist asthma centres].	LABA or any leukotriene-receptor antagonist, or theophylline (Level 4); or, regular oral steroid usage combined with ICS and LABA (Level 5).		exacerbation managed with mOCS and asthma-related hospital admission]	Exacerbation requiring hospitalisation (severe exacerbation)	0.33 [0.39]
Lloyd 2008 (167) UK	Members of the public (from which societal preferences for the symptom burden associated with moderate-to-severe asthma was elicited)	NR	N=88	SG	Complete control of moderate-to-severe asthma	0.784 (±0.060)
Niven 2016 (168) UK (APEX II study)	Patients with severe persistent allergic (IgE-mediated) asthma	Patients were prescribed omalizumab for the first time as part of normal clinical practice (n=22 centres)	N=258	EQ-5D	Severe persistent allergic (IgE-mediated) asthma	Baseline value for patients by weeks of omalizumab therapy 16 weeks, 0.59 [0.25] 8 months, 0.58 [0.26] 12 months, 0.58 [0.25]
Norman 2013 (153) UK	Patients uncontrolled at step 4, and in the process of moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy (EXALT trial (116))	Omalizumab add-on therapy to optimised standard step 4 or 5 GINA therapy Standard step 4 or 5 GINA therapy	N=NR	EQ-5D	Severe asthma (day to day asthma symptoms used in the model taken from standard care arm)	0.719 [0.026]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Pavord 2017 (169) UK	Data obtained from 2010–2011 UK National Health and Wellness Surveys identified 701 patients treated with ICS+LABA (moderate to severe disease severity)	NR	N=701	SF-12	Moderate to severe asthma-not well controlled	0.65
				SF-12	Moderate to severe asthma- well controlled	0.74
				SF-12	Moderate to severe asthma (controlled and not well controlled)	0.69
Thomson 2013 (170) UK	Patients with severe refractory asthma recruited to the BTS severe asthma registry	NR	N=760	EQ-5D	Never smokers with severe asthma (n=461)	Median 0.7 (IQR 0.5-0.9)
					Ex-smokers with severe asthma (n=210)	Median 0.5 (IQR 0.2-0.7)
					Current smokers with severe asthma (n=69)	Median 0.5 (IQR 0.1-0.7)
Wilson 2016 (171) US, Canada, Australia, Germany, UK (Mapping algorithm study)	Patients (≥ 12 years) with severe asthma	NR	N=658	EQ-5D	Severe asthma	0.80 [0.21]

Abbreviations: AQL-5D, Asthma Quality of Life Utility Index-5 Dimensions; BTS, British Thoracic Society; EQ-5D, European Quality of Life-5 Dimensions; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; GINA, Global Initiative for Asthma; HDM, house dust mite; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; ITT, intent-to-treat; NICE, National Institute for Health and Care Excellence; NR, not reported; OCS, oral corticosteroid; PP, per protocol; SABA, short-acting beta agonist; SF-12, 12-Item Short Form Health Survey; SG, standard gamble; SLIT, sublingual allergen immunotherapy; SLR, systematic literature review.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR (initial search on 6th November 2017, updated search on 23rd November 2021) was conducted to identify studies reporting on cost and healthcare resource use relevant to the decision problem (i.e. studies reporting health state utility values in patients aged ≥12 years with severe asthma).

Full details of the SLR methodology and results are provided in Appendix I.

In total across the original and updated cost and healthcare resource use SLR, ten full publication references and one conference abstract were included, resulting in a total of 11 studies eligible for inclusion. A tabulated overview of these 11 studies is provided in Appendix I. One of these studies, Willson et al 2014 (67) was used to inform costs and healthcare resource use in the model as it provided UK-specific estimates, and in a format that closely aligned with the model structure.

B.3.5.1 Treatment costs

Treatment costs were applied in the model as acquisition costs only. The model conservatively assumed that the cost of administration would be equal across all of the biologics considered and that there was no administrative burden associated with standard of care treatment.

The acquisition cost used for standard of care was an average of ten commonly used inhalers, weighted by their market share (Table 132).

Table 132: Market share analysis for SoC acquisition cost calculation

Intervention	Cost per inhaler	Unit	Strength	Dose/day	Cost/day	Market share
Fostair	£29.32	120	200/6	4	£0.98	25.10%
Flutiform	£45.56	120	10/250	4	£1.52	5.90%
Symbicort	£28.00	60	400/12	4	£1.87	28.30%
Duoresp	£28.00	60	320/9	4	£1.87	7.20%
Seretide Accuhaler	£32.74	60	50/500	2	£1.09	11.40%
Seretide Evohaler	£29.32	120	25/250	4	£0.98	9.50%
Relvar	£29.50	30	22/184	1	£0.98	5.70%
AirFluSal	£20.52	120	25/250	4	£0.68	0.00%
Sirdupla	£28.32	120	25/250	4	£0.94	6.90%
Sereflo	£29.32	120	25/250	4	£0.98	0.00%

Intervention	Cost per inhaler	Unit	Strength	Dose/day	Cost/day	Market share
Weighted average price per day					£1.34	
Weighted average 4-week cost					£37.41	

Abbreviations: SoC, standard of care.
Source: TA565 (90) and BNF (172).

Where drug dosing calculations were dependent on patient baseline characteristics, mean values from both the NAVIGATOR and SOURCE trials were used. The mean patient weight used was 77.84 kg and mean IgE level was 532 kUA/L.

Drug acquisition costs were applied in the model based on the frequency of doses as per the summary of product characteristics for each intervention, and, except for tezepelumab with its PAS price, were based on UK list prices (Table 133 and Table 134).

Table 133: Annual drug acquisition costs

Intervention	Mean	Source
Tezepelumab (PAS price)	[redacted]	
Benralizumab (list price)	£1,955.00	BNF 30 mg (172)
Dupilumab (list price)	£632.45	BNF 200 mg (172), per prefilled syringe
Mepolizumab (list price)	£840.00	BNF 100 mg (172)
Omalizumab (list price)	£768.45	BNF 450 mg (weight 77.84 kg, IgE 532) (172)
SoC	£37.41	Annual cost based on market share analysis TA565 (90)
OCS (cost per mg)	£0.003	Prednisolone 5 mg tablets; eMIT database (173)

Abbreviations: BNF, British National Formulary; OCS, oral corticosteroid; SoC, standard of care;

Table 134: Number of annual doses per intervention

Intervention	Number of annual doses	
	Year 1	Year 2 onwards
Tezepelumab	13.0	13.0
Benralizumab	8.0	6.5
Dupilumab	27.0	26.0
Mepolizumab	13.0	13.0
Omalizumab	26.0	26.0
SoC	13.0	13.0

Abbreviations: SoC, standard of care.
Source: Drug summary of product characteristics and BNF (172).

B.3.5.2 Disease management costs

Disease management costs were based on healthcare health state occupancy, with different costs assigned to the three exacerbation states. These costs were a function of healthcare resource use, based on the expected frequency of resource use for patients in each health state (Table 135) and their associated unit costs (Table 136). Resource use frequency values were sourced from Willson 2014 (67) with the base case utilising both the controlled and uncontrolled asthma resource use. Reported weekly values were grossed up to 4-weekly values for use in the model.

When a patient experienced an exacerbation event, the following assumptions were applied for costs:

- An mOCS burst incurred the healthcare resource use and associated costs of an exacerbation without hospitalisation for the duration of that exacerbation.
- An A&E visit incurred the healthcare resource use and associated costs of an exacerbation without hospitalisation for the duration of that exacerbation as well as a one-off cost of an A&E visit.
- Hospitalisation exacerbation incurred the HRU and associated costs of an exacerbation without hospitalisation for the duration of that exacerbation as well as a one-off cost for hospitalisation.

Table 135: Weekly healthcare resource use frequencies

Healthcare resource	Weekly resource use							
	Asthma state				Exacerbation state			
	Controlled asthma		Uncontrolled asthma		Exacerbation without hospitalisation		Exacerbation with hospitalisation	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
GP visit (inpatient)	0.03100	0.00310	0.14000	0.01400	1.37000	0.13700	0.59000	0.05900
Nurse visit (inpatient)	0.05000	0.00500	0.16000	0.01600	0.90000	0.09000	1.38000	0.13800
Specialist visit (inpatient)	0.01600	0.00160	0.09400	0.00940	0.34000	0.03400	1.76000	0.17600
GP visit (home)	0.00082	0.00008	0.02500	0.00250	0.22000	0.02200	0.10200	0.01020
Nurse visit (home)	0.00000	0.00000	0.00072	0.00007	0.00330	0.00033	0.00470	0.00047
Spirometry	0.02600	0.00260	0.04900	0.00490	0.29000	0.02900	0.46000	0.04600
Flu vaccine	0.02000	0.00200	0.02000	0.00200	0.00000	0.00000	0.00000	0.00000
Desensitisation of asthma use	0.00460	0.00046	0.00870	0.00087	0.00000	0.00000	0.00000	0.00000

Abbreviations: A&E, Accident and Emergency; GP, general practitioner; OCS, oral corticosteroid; SE, standard error.
Exacerbation without hospitalisation was applied to mOCS burst and A&E visit.
All standard errors were assumed to be 10% of the mean value.
Source: Willson 2014 (67).

Table 136: Healthcare resource use unit costs

Healthcare resource	Mean	SE	Source
One hour of nurse time	£55.00	£5.50	PSSRU 2021, hourly cost of band 6 nurse (174)
GP visit (inpatient)	£39.00	£3.90	PSSRU 2021, 9.22 minute appointment (174)
GP visit (home)	£100.62	£10.06	PSSRU 2021, cost of £4.30 informed the per minute cost of patient contact (174). PSSRU 2013 informed the length of an out of surgery consultation lasting 23.4 minutes
Nurse visit (outpatient)	£11.00	£1.10	PSSRU 2021, 15 minute GP nurse at £44.00 per hour (174)
Nurse visit (home)	£13.75	£1.38	PSSRU 2021, 15 minute with band 6 nurse at £55.00 per hour (174)
Respiratory specialist visit (outpatient)	£174.81	£17.48	National Cost Collection 2019/20 (175), weighted average of consultant led, currency codes WF01A and WF01B, service code 340. Inflated to 2021 costs using an inflation index of 1.031
Spirometry	£32.69	£3.27	Willson et al (67) inflated to 2021 costs using an inflation index of 1.159.
Flu vaccine	£7.33	£0.73	Willson et al (67) inflated to 2021 costs using an inflation index of 1.159.
Desensitisation of asthma use	£203.26	£20.33	Willson et al (67) inflated to 2021 costs using an inflation index of 1.159.
A&E visit	£179.41	£17.94	National Cost Collection 2019/20 (175), weighted average of emergency medicine, currency codes VB01Z to VB09Z, service code T01NA, To2NA, T03NA and T04NA. Inflated to 2021 costs using an inflation index of 1.031
Hospitalised exacerbation	£2,325.84	£232.58	National Cost Collection 2019/20 (175), weighted average of non-elective long stay, currency codes DZ15M, DZ15N and DZ15P.

Healthcare resource	Mean	SE	Source
			Inflated to 2021 costs using an inflation index of 1.031

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

B.3.5.3 OCS-related adverse event costs

In addition to costs arising from exacerbations, the model accounted for costs arising from the treatment of OCS-related adverse events. Costs of mOCS adverse events were sourced from the same study that informed mOCS adverse event frequency (a historical cohort study commissioned by AstraZeneca using the Optimum Patient Care Research Database [OPCRD] and the Clinical Practice Research Datalink [CPRD] database [AstraZeneca data on file 2017]). OCS-related adverse event costs used in the model are summarised in Table 137.

Table 137: mOCS-related adverse event cost by mOCS dose (cyclical cost)

Adverse event		Cyclical cost (£) by mOCS dose (mg/day)					
		0 to <0.5	0.5 to <2.5	2.5 to <5	5 to <7.5	7.5 to <15	>15
Type 2 diabetes mellitus	Mean	£20.38	£20.92	£24.02	£32.20	£30.23	£60.62
	SE	£1.03	£0.51	£1.30	£6.60	£5.25	£25.19
Osteoporosis	Mean	£20.63	£20.22	£20.27	£19.29	£25.01	£93.12
	SE	£0.36	£0.47	£2.23	£1.66	£3.49	£66.58
Glaucoma	Mean	£14.93	£17.02	£17.61	£18.01	£15.72	£13.65
	SE	£0.32	£0.53	£0.98	£1.43	£1.22	£2.33
Cataract	Mean	£31.66	£36.95	£50.73	£51.98	£42.50	£61.80
	SE	£1.34	£2.02	£5.01	£7.04	£7.53	£35.19
Myocardial infarction	Mean	£21.58	£21.98	£27.08	£36.79	£25.72	£64.91
	SE	£0.86	£0.88	£3.10	£7.31	£3.43	£27.68
Heart failure	Mean	£18.70	£21.49	£25.53	£27.00	£28.66	£48.22
	SE	£0.73	£1.03	£2.15	£3.51	£3.67	£23.73
Cerebrovascular accident	Mean	£25.69	£24.42	£30.60	£37.49	£32.66	£78.87
	SE	£1.35	£0.97	£3.47	£8.07	£4.06	£35.85
Renal impairment	Mean	£16.02	£17.28	£19.79	£26.82	£20.77	£31.45
	SE	£0.86	£0.69	£1.83	£6.03	£2.53	£15.31
Peptic ulcer	Mean	£10.05	£12.53	£14.04	£20.85	£17.15	£50.45
	SE	£0.26	£0.80	£0.68	£5.69	£1.61	£28.80
Pneumonia	Mean	£8.81	£13.93	£25.88	£28.28	£33.51	£49.28
	SE	£0.30	£0.43	£2.02	£5.08	£4.71	£13.85

Abbreviations: OCS, oral corticosteroid; SE, standard error.
Source: AZ data on file 2017.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

Please see Appendix P.

B.3.6.2 Assumptions

Table 138 lists the assumptions made in the model and their rationale.

Table 138: 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
All biologics were assumed to have same response rates as tezepelumab	No data to inform for other biologics
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.

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

The following analysis considers tezepelumab as an add-on to SoC treatment and (in totality) in 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 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 had 3 or more exacerbations in the prior year or who are on mOCS, and irrespective of biomarker values.

Incremental analyses are shown for the anti-IL-5 eligible patients in Table 139. An incremental analysis compares multiple mutually exclusive treatments against each other to find the most cost-effective treatment option out of all of the available comparators. This is implemented in a stepwise approach following the steps below:

- Comparators are ordered from the least to most expensive
- Comparators are compared for strong dominance. Comparators are dominated if they are both more costly and less effective than other comparators included in the analysis
- Comparators are compared for extended dominance. Comparators are extendedly dominated if an alternative comparator can provide more QALYs for a lower cost per QALY

In the fully incremental analyses for the anti-IL-5 eligible patients (Table 139), 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 139.

Base case pair-wise analyses for tezepelumab versus dupilumab and omalizumab are presented in Table 140 and Table 141, respectively.

Table 140 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 141 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.

Base case pair-wise analysis for tezepelumab versus SoC for the non-bio eligible population is presented in Table 142. Tezepelumab was associated with an incremental

cost of [redacted] and a QALY gain of [redacted], resulting in an ICER of £29,968 per QALY gained, just below the typically accepted £30,000 per QALY WTP threshold.

Clinical outcomes from the model, and disaggregated results of the base case cost-effectiveness analysis are provided in Appendix J.

B.3.7.1.1 Anti-IL-5 eligible population

Table 139: 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.

Figure 64: Cost-effectiveness plane (anti-IL-5 eligible)

Abbreviations: CE, cost-effectiveness; IL, interleukin.

B.3.7.1.2 Dupilumab eligible population

Table 140: 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.

Figure 65: Cost-effectiveness plane (dupilumab eligible)

[redacted]

Abbreviations: CE, cost-effectiveness;

B.3.7.1.3 Omalizumab eligible population

Table 141: 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.

Figure 66: Cost-effectiveness plane (omalizumab eligible)

[redacted]

Abbreviations: CE, cost-effectiveness;

B.3.7.1.4 Non-bio eligible population (3+ exacerbations OR mOCS)

Table 142: 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.

Figure 67: Cost-effectiveness plane (non-bio eligible [3+ exacerbations OR mOCS])

Abbreviations: CE, cost-effectiveness; mOCS, maintenance oral corticosteroid treatment.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The model was constructed and parameterised to enable probabilistic sensitivity analysis (PSA) to assess the uncertainty in the model inputs. Where appropriate, uncertainty was characterised through the use of standard statistical distributions. The parameters made probabilistic are provided in Appendix P.

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

B.3.8.1.1 Anti-IL-5 eligible population

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 both of the comparator biologics considered in the anti-IL-5 eligible population. Table 143 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 68. 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 69.

Table 143: 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]	[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.

Figure 68: Incremental cost-effectiveness scatter plot (anti-IL-5 eligible)

Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; PSA, probabilistic sensitivity analysis.

Figure 69: Cost-effectiveness frontier (anti-IL-5 eligible)

Abbreviations: CE, cost-effectiveness; IL, interleukin.

B.3.8.1.2 Dupilumab eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs whereas dupilumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs, equating to tezepelumab producing an additional [redacted] with a cost saving of [redacted] versus dupilumab (i.e. being dominant versus dupilumab). The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 144 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot provided in Figure 70. The incremental cost-effectiveness scatter plot shows that tezepelumab had 100% probability of being cost-effective at £20,000 and £30,000 per QALY gained versus dupilumab. The CEAC and CEAF are presented in Figure 71.

Table 144: 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.

Figure 70: Incremental cost-effectiveness scatter plot (dupilumab eligible)

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

Figure 71: Cost-effectiveness frontier (dupilumab eligible)

Abbreviations: CE, cost-effectiveness.

B.3.8.1.3 Omalizumab eligible population

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs whereas omalizumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs, equating to tezepelumab producing an additional [redacted] QALYs with a cost saving of [redacted] versus omalizumab (i.e. being dominant versus omalizumab). The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 145 presents the probabilistic incremental cost-effectiveness results in detail with the individual simulation scatter plot presented in Figure 72. The incremental cost-effectiveness scatter plot shows that tezepelumab had 100% probability of being cost-effective at £20,000 and £30,000 per QALY gained versus omalizumab. The CEAC and CEAF are presented in Figure 73.

Table 145: 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.

Figure 72: Incremental cost-effectiveness scatter plot (omalizumab eligible)

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

Figure 73: Cost-effectiveness frontier (omalizumab eligible)

Abbreviations: CE, cost-effectiveness.

B.3.8.1.4 Non-bio eligible population (3+ exacerbations OR mOCS)

Tezepelumab accumulated total (discounted) costs of [redacted] and [redacted] QALYs, whereas SoC accumulated total (discounted) costs of [redacted] and [redacted] QALYs, equating to tezepelumab producing an additional [redacted] QALYs at an incremental cost of [redacted] versus SoC. This results in tezepelumab being cost-effective versus SoC with an ICER of [redacted] per QALY. The probabilistic results were highly comparable with the base case deterministic results, demonstrating that the model is stable. Table 146 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot presented in Figure 74. The incremental cost-effectiveness scatter plot shows that tezepelumab had [redacted] probability of being cost-effective at £20,000 per QALY gained and [redacted] at £30,000 per QALY gained. The CEAC and CEAF are presented in Figure 75.

Table 146: 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.

Figure 74: 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 75: 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.

B.3.8.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (DSAs) were conducted by varying the input for all parameters in the model, whilst keeping all other inputs the same. For certain parameters where estimates of precision were available, the lower and upper limits were defined by the 95% CI around the mean. If no measure of uncertainty was available, the parameter was varied by ±10% of their base case mean value.

Since a negative ICER can in some instances be challenging to interpret, all scenarios described below used a univariate analysis based on a net monetary benefit (NMB) method assuming a WTP threshold of £30,000 per QALY. In addition, the ICER was considered for the non-bio eligible (3+ exacerbations OR mOCS) subgroup. In these scenarios, the NMB was recorded for each upper and lower value, and the ten parameters with the highest impact on the NMB were used to produce a tornado diagram displaying the results of the DSA. (Note that all model parameters were considered, only the ten most influential are presented for simplicity).

B.3.8.2.1 Anti-IL-5 eligible population

Table 147: Results of one-way deterministic sensitivity analysis (anti-IL-5 eligible vs benralizumab)

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Base case NMB	[redacted]	
Natural Discontinuation Rate (Cyclical) (with OCS) - Benralizumab (0.006 to 0.020; base case 0.013)	[redacted]	[redacted]
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Benralizumab (1.06 to 2.28; base case 1.67)	[redacted]	[redacted]
Baseline mOCS - Proportion on mOCS (0.52 to 0.78; base case 0.65)	[redacted]	[redacted]
Probability of Discontinuation at Response Week (with OCS) - Benralizumab (0.000 to 0.100; base case 0.048)	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab (0.006 to 0.020; base case 0.013)	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (without OCS) - Benralizumab (0.006 to 0.007; base case 0.007)	[redacted]	[redacted]
Teze Exac. Split - Hosp (Uncontrolled With OCS) (0.0% to 24.0%; base case 8.3%)	[redacted]	[redacted]
Probability of Discontinuation at Response Week (without OCS) - Benralizumab (0.000 to 0.100; base case 0.048)	[redacted]	[redacted]

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
OCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation) (0.47 to 0.79; base case 0.63)	[redacted]	[redacted]
Post-Assessment With mOCS Teze TP - Uncontrolled Exacerbation -> Uncontrolled Asthma (50.5% to 99.5%; base case 75.0%)	[redacted]	[redacted]

Abbreviations: Hosp, hospitalisation; IL, interleukin; mOCS, maintenance oral corticosteroid treatment; NMB, net monetary benefit.

Figure 76: Results of one-way deterministic sensitivity analysis (anti-IL-5 eligible vs benralizumab)

Abbreviations: IL, interleukin; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; OCS, oral corticosteroid.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

Table 148: Results of one-way deterministic sensitivity analysis (anti-IL-5 eligible vs mepolizumab)

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Base case NMB	[redacted]	
Natural Discontinuation Rate (Cyclical) (with OCS) - Mepolizumab (0.006 to 0.020; base case 0.013)	[redacted]	[redacted]
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Mepolizumab (0.36 to 1.88; base case 1.12)	[redacted]	[redacted]

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
SoC Exac. Split - Hosp (Uncontrolled With OCS) (3.0% to 28.2%; base case 15.6%)	[redacted]	[redacted]
With mOCS SoC TP - Uncontrolled Asthma -> Uncontrolled Exacerbation (10.2% to 22.9%; base case 16.5%)	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab (0.006 to 0.020; base case 0.013)	[redacted]	[redacted]
Baseline mOCS - Proportion on mOCS (0.52 to 0.78; base case 0.65)	[redacted]	[redacted]
With mOCS SoC TP - Controlled Asthma -> Controlled Exacerbation (11.5% to 28.5%; base case 20.0%)	[redacted]	[redacted]
mOCS Sparing Relative Reduction Odds Ratio (Vs. Tezepelumab) - Odds Ratio ≥90% Reduction (Discontinuation) (Mepolizumab) (-0.03 to 0.69; base case 0.33)	[redacted]	[redacted]
With mOCS SoC TP - Uncontrolled Exacerbation -> Controlled Asthma (1.9% to 32.9%; base case 17.4%)	[redacted]	[redacted]
Probability of Discontinuation at Response Week (with OCS) - Mepolizumab (0.000 to 0.100; base case 0.048)	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; IL, interleukin; NMB, net monetary benefit; OCS, oral corticosteroid; SoC, standard of care.

Figure 77: Results of one-way deterministic sensitivity analysis (anti-IL-5 eligible vs mepolizumab)

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; IL, interleukin; NMB, net monetary benefit; OCS, oral corticosteroid; SoC, standard of care.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

B.3.8.2.2 Dupilumab eligible population

Table 149: Results of one-way deterministic sensitivity analysis (dupilumab eligible)

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Base case NMB	[redacted]	
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Dupilumab (-0.03 to 3.31; base case 1.64)	[redacted]	[redacted]
Teze Exac. Split - Hosp (Uncontrolled Without OCS) (0.0% to 16.1%; base case 5.6%)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Uncontrolled Exacerbation -> Controlled Asthma (0.0% to 35.8%; base case 17.6%)	[redacted]	[redacted]
Relative Annual Hospitalisation Rate (Vs. Tezepelumab) - Dupilumab (1.21 to 4.35; base case 2.78)	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (without OCS) - Dupilumab (0.006 to 0.007; base case 0.007)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Uncontrolled Exacerbation -> Uncontrolled Asthma (48.9% to 92.2%; base case 70.6%)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Uncontrolled Asthma -> Uncontrolled Exacerbation (6.8% to 18.9%; base case 12.8%)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Controlled Exacerbation -> Controlled Asthma (0.0% to 100.0%; base case 50.0%)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Controlled Asthma -> Controlled Exacerbation (0.0% to 5.3%; base case 2.2%)	[redacted]	[redacted]
Post-Assessment Without mOCS Teze TP - Controlled Asthma -> Uncontrolled Asthma (3.0% to 14.9%; base case 9.0%)	[redacted]	[redacted]

Abbreviations: Exac, exacerbation; Hosp, hospitalisation; NMB, net monetary benefit; OCS, oral corticosteroid; Teze, tezepelumab.

Figure 78: Results of one-way deterministic sensitivity analysis (dupilumab eligible)

Abbreviations: Exac, exacerbation; Hosp, hospitalisation; NMB, net monetary benefit; OCS, oral corticosteroid; Teze, tezepelumab.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

B.3.8.2.3 Omalizumab eligible population

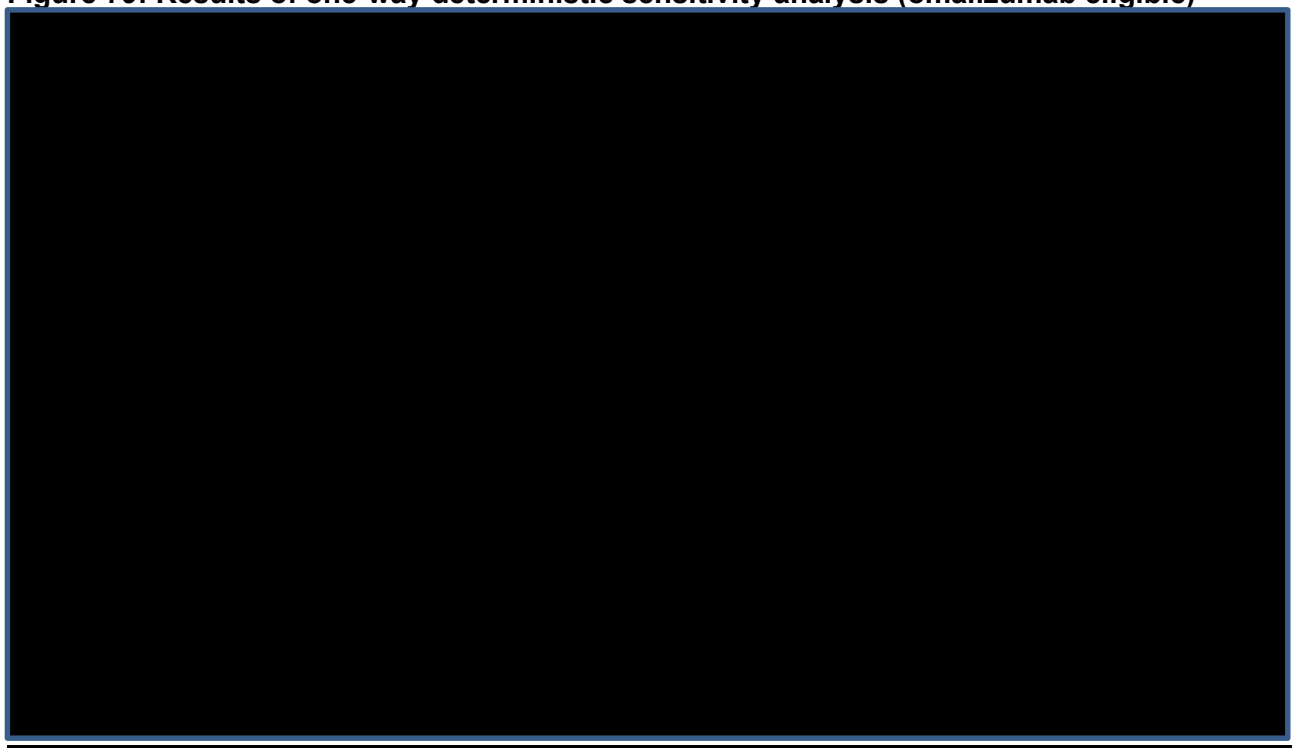
Table 150: Results of one-way deterministic sensitivity analysis (omalizumab eligible)

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Base case NMB		
Natural Discontinuation Rate (Cyclical) (with OCS) - Omalizumab (0.006 to 0.020; base case 0.013)		
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Omalizumab (0.86 to 2.42; base case 1.64)		
Probability of Discontinuation at Response Week (without OCS) - Omalizumab (0.003 to 0.115; base case 0.059)		
Natural Discontinuation Rate (Cyclical) (without OCS) - Omalizumab (0.006 to 0.007; base case 0.007)		
Probability of Discontinuation at Response Week (with OCS) - Omalizumab (0.003 to 0.115; base case 0.059)		
Relative Annual Hospitalisation Rate (Vs. Tezepelumab) - Omalizumab (1.13 to 3.87; base case 2.50)		
Baseline mOCS - Proportion on mOCS (0.36 to 0.53; base case 0.45)		

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Teze Exac. Split - Hosp (Controlled Without OCS) (0.0% to 18.1%; base case 6.3%)	[redacted]	[redacted]
OCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation) (0.43 to 0.69; base case 0.56)	[redacted]	[redacted]
OCS Sparing Reduction Teze - Proportion with 50% - <75% (0.07 to 0.26; base case 0.16)	[redacted]	[redacted]

Abbreviations: Hosp, hospitalisation; NMB, net monetary benefit; OCS, oral corticosteroid; Teze, tezepelumab.

Figure 79: Results of one-way deterministic sensitivity analysis (omalizumab eligible)



Abbreviations: Exac, exacerbation; Hosp, hospitalisation; NMB, net monetary benefit; OCS, oral corticosteroid; Teze, tezepelumab.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

B.3.8.2.4 Non-bio eligible population (3+ exacerbations OR mOCS)

Table 151: Results of one-way deterministic sensitivity analysis (Non-bio eligible [3+ Exacs OR mOCS])

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
Base case NMB	£24	
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Controlled Asthma -> Uncontrolled Asthma (7.5% to 15.0%; base case 11.2%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Uncontrolled Asthma -> Uncontrolled Exacerbation (12.4% to 19.9%; base case 16.2%)	[redacted]	[redacted]

Variable (lower bound to upper bound; base case value)	NMB with lower bound	NMB with upper bound
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Controlled Asthma -> Controlled Exacerbation (3.3% to 9.0%; base case 6.2%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: SoC Exac. Split - Hosp (Uncontrolled Without OCS) (8.7% to 24.6%; base case 16.7%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Uncontrolled Exacerbation -> Controlled Asthma (5.8% to 21.6%; base case 13.7%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Uncontrolled Asthma -> Controlled Asthma (11.4% to 18.7%; base case 15.1%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: SoC Exac. Split - A&E visit (Controlled Without OCS) (0.0% to 24.3%; base case 10.5%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without mOCS SoC TP - Uncontrolled Exacerbation -> Uncontrolled Asthma (51.9% to 74.1%; base case 63.0%)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: mOCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation) (0.01 to 0.50; base case 0.25)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab (0.006 to 0.020; base case 0.013)	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; mOCS, maintenance oral corticosteroid treatment; OCS, oral corticosteroid; SoC, standard of care; Teze, tezepelumab.

Figure 80: Results of one-way deterministic sensitivity analysis (Non-bio eligible [3+ Exacs OR mOCS])

Abbreviations: Exac, exacerbations; Hosp, hospitalisation; mOCS, maintenance oral corticosteroid treatment; NMB, net monetary benefit; OCS, oral corticosteroid; SoC, standard of care; Teze, tezepelumab.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

In the anti-IL-5 eligible, dupilumab eligible, and omalizumab eligible analyses, tezepelumab resulted in a positive NMB across all parameters and ranges considered. In the non-bio eligible cohort, the baseline ICER vs SoC was £29,968 per QALY.

[redacted]

Figure 81: Results of one-way deterministic sensitivity analysis showing ICER (Non-bio eligible [3+ Exacs OR mOCS])

Abbreviations: Exac, exacerbations; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroid treatment; NMB, net monetary benefit; OCS, oral corticosteroid; SoC, standard of care; Teze, tezepelumab.
Light blue = NMB lower bound. Dark blue = NMB upper bound.

B.3.8.3 Threshold analysis

A threshold analysis was performed on the top ten model parameters (as identified in the univariate sensitivity analysis above) to determine at which values tezepelumab would no longer be considered cost-effective at a WTP threshold of £30,000 per QALY (Table 152 to Table 156). In this analysis, all other parameters were kept at their original value.

Table 152: Results of threshold analysis (anti-IL-5 eligible vs benralizumab)

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
anti-IL-5 eligible: Natural Discontinuation Rate (Cyclical) (with OCS) - Benralizumab	[redacted]	[redacted]
anti-IL-5 eligible: Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Benralizumab	[redacted]	[redacted]
anti-IL-5 eligible: Baseline mOCS - Proportion on OCS	[redacted]	[redacted]
anti-IL-5 eligible: Probability of Discontinuation at Response Week (with OCS) - Benralizumab	[redacted]	[redacted]
anti-IL-5 eligible: Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab	[redacted]	[redacted]
anti-IL-5 eligible: Natural Discontinuation Rate (Cyclical) (without OCS) - Benralizumab	[redacted]	[redacted]
anti-IL-5 eligible: Teze Exac. Split - Hosp (Uncontrolled With OCS)	[redacted]	[redacted]
anti-IL-5 eligible: Probability of Discontinuation at Response Week (without OCS) - Benralizumab	[redacted]	[redacted]
anti-IL-5 eligible: mOCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation)	[redacted]	[redacted]

Abbreviations: Exac, exacerbation; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; IL, interleukin; NA, not applicable; OCS, oral corticosteroid; QALY, quality-adjusted life year.
† Outside plausible range.

Table 153: Results of threshold analysis (anti-IL-5 eligible vs mepolizumab)

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
Natural Discontinuation Rate (Cyclical) (with OCS) - Mepolizumab	[redacted]	[redacted]
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Mepolizumab	[redacted]	[redacted]
SoC Exac. Split - Hosp (Uncontrolled With OCS)	[redacted]	[redacted]
With mOCS SoC TP - Uncontrolled Asthma -> Uncontrolled Exacerbation	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab	[redacted]	[redacted]
Baseline mOCS - Proportion on OCS	[redacted]	[redacted]
With OCS SoC TP - Controlled Asthma -> Controlled Exacerbation	[redacted]	[redacted]
OCS Sparing Relative Reduction Odds Ratio (Vs. Tezepelumab) - Odds Ratio ≥90% Reduction (Discontinuation) (Mepolizumab)	[redacted]	[redacted]

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
With OCS SoC TP - Uncontrolled Exacerbation -> Controlled Asthma	[redacted]	[redacted]
Probability of Discontinuation at Response Week (with OCS) - Mepolizumab	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; IL, interleukin; NA, not applicable; OCS, oral corticosteroid; QALY, quality-adjusted life year; SoC, standard of care.
† Outside plausible range.

Table 154: Results of threshold analysis (dupilumab eligible)

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Dupilumab	[redacted]	[redacted]
Teze Exac. Split - Hosp (Uncontrolled Without OCS)	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Uncontrolled Exacerbation -> Controlled Asthma	[redacted]	[redacted]
Relative Annual Hospitalisation Rate (Vs. Tezepelumab) - Dupilumab	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (without OCS) - Dupilumab	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Uncontrolled Exacerbation -> Uncontrolled Asthma	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Uncontrolled Asthma -> Uncontrolled Exacerbation	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Controlled Exacerbation -> Controlled Asthma	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Controlled Asthma -> Controlled Exacerbation	[redacted]	[redacted]
Post-Assessment Without OCS Teze TP - Controlled Asthma -> Uncontrolled Asthma	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; NA, not applicable; OCS, oral corticosteroid; QALY, quality-adjusted life year; SoC, standard of care.

Table 155: Results of threshold analysis (omalizumab eligible)

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
Natural Discontinuation Rate (Cyclical) (with OCS) - Omalizumab	[redacted]	[redacted]
Relative Annual Exacerbation Rate (Vs. Tezepelumab) - Omalizumab	[redacted]	[redacted]
Probability of Discontinuation at Response Week (without OCS) - Omalizumab	[redacted]	[redacted]
Natural Discontinuation Rate (Cyclical) (without OCS) - Omalizumab	[redacted]	[redacted]
Probability of Discontinuation at Response Week (with OCS) - Omalizumab	[redacted]	[redacted]
Relative Annual Hospitalisation Rate (Vs. Tezepelumab) - Omalizumab	[redacted]	[redacted]
Baseline OCS - Proportion on OCS	[redacted]	[redacted]
Teze Exac. Split - Hosp (Controlled Without OCS)	[redacted]	[redacted]
OCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation)	[redacted]	[redacted]
OCS Sparing Reduction Teze - Proportion with 50% - <75%	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; NA, not applicable; OCS, oral corticosteroid; QALY, quality-adjusted life year; SoC, standard of care.
† Outside plausible range.

Table 156: Results of threshold analysis (Non-bio eligible [3+ Exacs OR mOCS])

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Controlled Asthma -> Uncontrolled Asthma	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Uncontrolled Asthma -> Uncontrolled Exacerbation	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Controlled Asthma -> Controlled Exacerbation	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: SoC Exac. Split - Hosp (Uncontrolled Without OCS)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Uncontrolled Exacerbation -> Controlled Asthma	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Uncontrolled Asthma -> Controlled Asthma	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: SoC Exac. Split - A&E visit (Controlled Without OCS)	[redacted]	[redacted]

Variable	Base case (Lower bound to Upper bound)	Value to achieve ICER of £30,000 per QALY
3+ Exacs OR mOCS, non-bio eligible: Without OCS SoC TP - Uncontrolled Exacerbation -> Uncontrolled Asthma	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: OCS Sparing Reduction Teze - Proportion with 90% - 100% (Discontinuation)	[redacted]	[redacted]
3+ Exacs OR mOCS, non-bio eligible: Natural Discontinuation Rate (Cyclical) (with OCS) - Tezepelumab	[redacted]	[redacted]

Abbreviations: A&E, Accident and Emergency; Exac, exacerbation; Hosp, hospitalisation; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroid treatment; NA, not applicable; OCS, oral corticosteroid; QALY, quality-adjusted life year; SoC, standard of care.

In the anti-IL-5 eligible, dupilumab eligible, and omalizumab eligible cohort, when parameters were considered individually (and all other parameters remained unchanged), no plausible values could be identified that would result in an ICER of £30,000 per QALY. Note that, the Excel Goal Seek functionality used to perform the threshold analysis can generate illogical answers, although mathematically correct. All such illogical outcomes have been indicated in the respective tables.

[redacted]

B.3.8.4 Scenario analyses

In order to understand the importance of key assumptions within the model on the cost-effectiveness results, a number of scenario analyses were undertaken.

For all the below scenarios, results are provided for the anti-IL-5 eligible population in the comparison versus mepolizumab and benralizumab, the dupilumab NICE-reimbursed population in the comparison versus dupilumab, the omalizumab NICE-recommended population in the comparison versus omalizumab, and the non-bio eligible population versus SoC.

Scenario analyses undertaken included:

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

B.3.8.4.1 Alternative exacerbation-related mortality

The base case approach to deriving exacerbation-related mortality is described at Section B.3.3.4.2.

Scenario analyses were performed, whereby all-cause mortality in the model was calibrated to all-cause mortality in severe asthma patients reported in a real-world study. Asthma exacerbation-related mortality was adjusted in the model, to achieve the all-cause mortality calibration. The same study was used by the company in the dupilumab NICE appraisal, to validate all-cause mortality predicted by the company model.[b]

A 2019 case-control study in France using medical claims data estimated a 3-year severe asthma mortality of 7.1% (176). For this study a total of 690 patients with severe asthma were identified in a claims database and followed for 3 years. The mean age at index was 61 years and 34.3% of patients were male. The study reported that 58.7% of patients had used OCS in the study period, however the mean number of prescriptions dispensed over one year to these patients was 3.3, indicating that only a subset of patients was in receipt of OCS for maintenance use. No further baseline characterises used in the model were reported, so for the calibration, age and the percentage of male patients were adjusted to reflect Bourdin et al., with other model baseline characteristics remaining at their default values. Given the data collection period in Bourdin et al. pre-dated the introduction of most biologic treatments, it was only appropriate to calibrate to the SoC arm of the model, meaning this approach was only explored for the Non-bio eligible (3+ exacerbations OR mOCS) population.

Three-year mortality in the equivalent population in the model was found to be [redacted]%, substantially lower than that reported in Bourdin et al. (7.1%) (176).

It should be noted that the French Bourdin et al. study included a severe asthma all-comers population, without any restriction on exacerbation rates or asthma control. Therefore, given the higher disease burden in the target population for this appraisal, a higher 3-year mortality rate would be expected versus that reported by Bourdin et al. In keeping with this, a further scenario was conducted whereby the model delivered 50%

[b] NICE Dupilumab Committee Papers 2. Available at: https://www.nice.org.uk/guidance/ta751/documents/committee-papers-2 (accessed on 19th May 2022)

higher 3-year mortality (i.e.10.65%), than was reported in Bourdin et al., for an equivalent population.

In making the calibration adjustment to exacerbation-related mortality, mortality for all types of exacerbation (OCS burst, A&E visit, hospitalisation) and for all age bands was uplifted by a common multiplier to achieve the desired 3-year all-cause mortality in the SoC arm of the model, as can be seen at Table 157.

Table 157: Exacerbation-related mortality inputs used in the scenarios and resultant mortality

	Base Case	Bourdin et al.	Bourdin et al. + 50%
Multiplier	1	[redacted]	[redacted]
OCS burst			
Patients aged 18–44	[redacted]	[redacted]	[redacted]
Patients aged 45+	[redacted]	[redacted]	[redacted]
A&E visit			
Patients aged 18–44	[redacted]	[redacted]	[redacted]
Patients aged 45+	[redacted]	[redacted]	[redacted]
Hospitalisation			
Patients aged 18–24	[redacted]	[redacted]	[redacted]
Patients aged 25–34	[redacted]	[redacted]	[redacted]
Patients aged 35–44	[redacted]	[redacted]	[redacted]
Patients aged 45–54	[redacted]	[redacted]	[redacted]
Patients aged 55–64	[redacted]	[redacted]	[redacted]
Patients aged 65+	[redacted]	[redacted]	[redacted]
Resultant 3-year mortality, SoC (starting age 61, males = 34.3%)	[redacted]	[redacted]	[redacted]

Abbreviations: OCS, oral corticosteroids; Soc, Standard of care

Once the model was calibrated, starting age and the percentage of male patients were reset to default values and the model was run.

Results for the scenarios can be seen at Table 158 and Table 159.

Table 158: Scenario – mortality calibration to Bourdin et al. (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£21,091***

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

Table 159: Scenario – mortality calibration to Bourdin et al. + 50% (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]		-	-	-
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,793**

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

With all-cause mortality calibrated to Bourdin et al., the ICER versus SoC in the non-bio eligible (3+ exacerbations OR mOCS) population was reduced from £ 29,968 to £ 21,091 and fell further to £16,793 when employing the assumption that mortality would be 50% higher in the target population, owing to its greater disease burden.

The mortality calibration exercise suggests that all-cause mortality may be underestimated in the model versus real world outcomes, meaning that the base case ICER in the non-bio eligible (3+ exacerbations OR mOCS) is likely to be conservative.

Three-year mortality as predicted by the model for other populations considered in this appraisal can be seen at Table 160.

Table 160: 3-year mortality in the model for a cohort with starting age 61, with 34.3% males

Population	Technology	3-year mortality
Non-bio eligible (3+ exacerbations OR mOCS)	SoC	[redacted]
IL-5 eligible	Benralizumab	[redacted]
	Mepolizumab	[redacted]
Dupilumab eligible	Dupilumab	[redacted]
Omalizumab eligible	Omalizumab	[redacted]

Abbreviations: IL, interleukin; mOCS, maintenance oral corticosteroids; SoC, standard of care.

Owing to the magnitude of the difference in 3-year mortality between model base case and the French real-world study ([redacted]% vs. 7.1%, RR [redacted]), it is likely that cost-effectiveness estimates for tezepelumab vs. other biologics in their respective populations are also likely to be conservative (given the NMA for AAER favours tezepelumab), as had Bourdin et al. (176) been conducted at a later time when biologics were more widely available, it seems highly unlikely that 3-year all-cause mortality would have fallen to levels predicted by the model.

B.3.8.4.2 Alternative baseline characteristics

In the model base case, Jackson 2021 (73) 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 (see Table 161).

Table 161: Alternative patient baseline characteristics (from NAVIGATOR and SOURCE)

Parameter	Mean	SE	Source
anti-IL-5 eligible			
Age (years)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage male (%)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage mOCS users (%)	[redacted]	[redacted]	SOURCE
mOCS baseline dose (mg/day)	[redacted]	[redacted]	SOURCE
Dupilumab eligible			
Age (years)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage male (%)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage mOCS users (%)	[redacted]	[redacted]	NICE recommends only the 200 mg dose of dupilumab, which is not licensed for patients receiving mOCS
mOCS baseline dose (mg/day)	[redacted]	[redacted]	SOURCE
Omalizumab eligible			
Age (years)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage male (%)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage mOCS users (%)	[redacted]	[redacted]	SOURCE
mOCS baseline dose (mg/day)	[redacted]	[redacted]	SOURCE
Non-bio eligible (3+ exacerbations OR mOCS)			
Age (years)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage male (%)	[redacted]	[redacted]	NAVIGATOR + SOURCE
Percentage mOCS users (%)	[redacted]	[redacted]	SOURCE
mOCS baseline dose (mg/day)	[redacted]	[redacted]	SOURCE

Abbreviations: IL, interleukin; mOCS: maintenance oral corticosteroid treatment; NICE, National Institute for Health and Care Excellence; SE: standard error.

Table 162: Scenario – alternative patient characteristics (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	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 163: Scenario – alternative patient characteristics (dupilumab eligible)

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

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

Table 164: Scenario – alternative patient characteristics (omalizumab eligible)

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

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

Table 165: Scenario – alternative patient characteristics (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,937**

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.

In NAVIGATOR and SOURCE, the proportion of patients on mOCS was lower than reported in Jackson 2021 (73) which reflect current practice in the UK. With lower rates of discontinuation associated with those not receiving mOCS, more patients remain on biologic treatment resulting in slightly higher costs. In addition, there is also a smaller cohort who can benefit from mOCS sparing. However, 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 increasing marginally from £29,968 to £30,937

B.3.8.4.3 Alternative discount rates

The base case analysis assumed costs and outcomes were discounted at 3.5% in line with the NICE Guide to the Methods of Technology Appraisal 2013 (160). The current 3.5% is based on recommendations from the UK Treasury for discounting of costs in the Green Book (177). The Green Book applies a standard discount rate of 3.5% per annum to future benefits and costs. However, a reduced rate of 1.5% per annum applies to policies that impact health or life outcomes. This means that future health and life benefits are not reduced by as much as other future benefits when performing benefit-cost ratios. This particular scenario used the reduced discount rate of 1.5% per annum for costs and outcomes.

Table 166: Scenario – alternative discount rate (anti-IL-5 eligible)

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

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	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 167: Scenario – alternative discount rate (dupilumab eligible)

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

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

Table 168: Scenario – alternative discount rate (omalizumab eligible)

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

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

Table 169: Scenario – alternative discount rate (non-bio eligible [3+ exacerbations OR mOCS])

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,897

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.

With a lower discount rate, the absolute costs and QALYs increase for all treatment arms in all 4 patient cohorts. In the anti-IL-5 eligible, dupilumab eligible and omalizumab eligible cohorts tezepelumab remains the dominant treatment choice. In the non-bio eligible cohort, the ICER decreases from £29,968 to £25,897.

B.3.8.4.4 Alternative comparative exacerbation rates

Anti-IL-5 eligible

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 appraisal (90).

Table 170: Alternative relative annual exacerbation rate (anti-IL-5 eligible)

Intervention	Relative annual exacerbation rates vs tezepelumab + SoC	
	Mean	Source
Benralizumab + SoC	[redacted]	≥3 Exacs in prior 12 months subgroup NMA (Section B.2.9.2.1.5)
Mepolizumab + SoC	[redacted]	

Abbreviations: Exacs, exacerbations; IL, interleukin; NMA, network meta-analysis; SE, standard error; SoC, standard of care.
† Assumed equivalence to benralizumab

Table 171: Scenario – Alternative annual exacerbation rate (anti-IL-5 eligible)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	Incremental ICER (£/QALY)	ICER versus baseline (£/QALY)
Tezepelumab (PAS price) + SoC	[redacted]	[redacted]	[redacted]	-	-	-		
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Benralizumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£211,560	Dominated

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

Dupilumab eligible

In the base case, the relative exacerbation rate data for the dupilumab eligible cohort was derived from the NMA data relating to the EOS Low: <300 cells/μL subgroup. This scenario considered three alternative data NMA subgroups:

1. FeNO High: ≥25 ppb subgroup NMA data
2. ≥3 Exacerbations in last 12 months subgroup NMA data
3. EOS High: ≥150 cells/μL subgroup NMA data

Table 172: Alternative relative annual exacerbation rate (dupilumab eligible)

Intervention	Relative annual exacerbation rates vs tezepelumab + SoC	
	Mean	Source
Dupilumab + SoC	1.15	High FeNO level (≥25 ppb) NMA (Section B.2.9.2.1.6)
Dupilumab + SoC	[redacted]	≥3 Exacs in last 12 months subgroup NMA (Section B.2.9.2.1.5)
Dupilumab + SoC	1.10	EOS High: ≥150 cells/μL subgroup NMA (Section B.2.9.2.1.1)

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

Table 173: Scenario – Alternative (1) relative annual exacerbation rate (dupilumab eligible)

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

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

Table 174: Scenario – Alternative (2) relative annual exacerbation rate (dupilumab eligible)

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

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

Table 175: Scenario – Alternative (3) relative annual exacerbation rate (dupilumab eligible)

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

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

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

In these scenarios, tezepelumab remained the dominant treatment choice.

B.3.8.5 Summary of sensitivity analyses results

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 [redacted] of simulations, increasing to [redacted] at a cost-effectiveness threshold of £30,000 per QALY.

In the anti-IL-5 eligible, dupilumab eligible, and omalizumab eligible cohorts, the most influential parameters in deterministic sensitivity analysis tended to be discontinuation and the relative annual exacerbation rate. However, it should be noted that, in the base case, the analysis assumed equivalent discontinuation rates across the biologics. As such, the univariate analysis is of limited value. In all comparisons across these three cohorts, tezepelumab resulted in a positive NMB and so remained the cost-effective treatment of choice.

In the non-bio eligible cohort, the most influential parameters related to the model transition probabilities, likely influenced by the relative low numbers and associated wide confidence intervals. Despite this, the relative impact of these parameters was small, resulting in variation in NMB of between [redacted].

The effects of other model parameters on the base case ICER were found to be modest and the extensive scenario analyses demonstrated the robustness of the base case ICERs.

B.3.9 Subgroup analysis

Given it was necessary to stratify the model patient population into post hoc subgroups in order to meet the NICE decision problem (see Section B.3.2.1), no further subgroup analyses are provided.

B.3.10 Validation

During the iterative process of the economic evaluation development, the model underwent interim QCs by the model developers. Furthermore, the model also underwent an additional review and QC during the development process by a third-party vendor. A QA was also performed internally by an AZ analyst and covered a critique of the following:

- Completeness of model documentation and availability of the model (Excel/VBA application)
- General checklist of validity and credibility of the model
- Completeness and accuracy of reporting of model results

B.3.11 Interpretation and conclusions of economic evidence

No published studies were identified to address the NICE scope. The most relevant cost effectiveness analyses were the benralizumab, dupilumab, mepolizumab, and reslizumab NICE HTA submissions; however, as all have been recommended with commercially sensitive PAS, the level of information available did not allow for a comparison of the results.

Although the label for tezepelumab encompasses adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose ICS and an additional controller, the analyses presented as part of this submission focused on patients who had experienced 3 or more exacerbations in the prior year OR who were on mOCS.

Assumptions in the model surrounding mortality, the source of utilities, and the length of treatment duration were aligned with previous STAs in the disease area.

Costs and outcomes were estimated based on the most relevant sources for England and the model structure and parameters were validated with clinical experts to ensure relevance to England.

The main strength of the model is that it reflects the two main dimensions of asthma, those being symptoms and exacerbations. For the comparison to SoC, these dimensions were

captured through the main clinical trials used to assess the clinical effectiveness: NAVIGATOR and SOURCE. For comparisons with other biologic therapies not included in the clinical trial, ITC methods were used to assess the relative performance of tezepelumab in the reduction of exacerbations, hospitalisation, and OCS dose.

The main limitations of the model are summarised below:

- The data from NAVIGATOR and SOURCE were stratified to align with NICE's previous recommendations for biologics treatment in this disease area. In some instances, the resulting patient subgroups were small and consequently uncertainty increased.
- There was no direct comparative efficacy evidence with other biologic therapies. Asthma control was likely a key driver in the model, but with no data to inform this probability for other biologics, it was assumed that all biologics had equal efficacy in this regard – something which may favour comparators given the positive results of tezepelumab.
- Given the lack of data related to exacerbations and asthma-related deaths reported in the clinical trials, it was necessary to use secondary sources of information.
- The long-term costs and consequences of mOCS use may be underestimated by the Norman 2013 (153) and OPRI data (AstraZeneca data on file 2017) as not all chronic conditions are included.

The waning of treatment effect was not included in the model. However, given that there is no evidence to suggest that there is a loss of efficacy over time, and that previous appraisals in this area also did not include this effect, we believe this approach is justified.

The results from the economic analysis show tezepelumab, as an add-on to SoC treatment, can be considered to be a dominant treatment option (versus comparator list prices) for anti-IL-5 eligible patients (those currently treated with either benralizumab and mepolizumab), dupilumab eligible patients, and omalizumab patients – all 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. These results do not vary significantly in scenario and sensitivity analyses.

In addition, in the cohort of patients currently considered non-bio eligible, tezepelumab, when compared with SoC alone, had an ICER slightly lower than the £30,000 threshold at

£29,968 per QALY gained. This result was stable through sensitivity and scenario analyses.

The findings of the economic model can be regarded as conservative for tezepelumab, given:

- The model may underestimate real-world asthma-related mortality
- The model may underestimate the relative efficacy of tezepelumab versus other biologics in relation to asthma control
- The model includes 10 AEs stemming mOCS use. Other mOCS-related AEs such as mental health conditions and weight gain which would also be expected to impact costs and HRQoL are not captured. As such the model is likely to be conservative for tezepelumab vs. SoC in the non-bio eligible (3+ exacerbations OR mOCS) population in this regard
- Tezepelumab is the only biologic to show a benefit on airway hyperresponsiveness, which is associated with poorer quality of life (44), meaning the assumption that the treatment effect on utility for each comparator biologic was equivalent to that of tezepelumab may favour biologic comparator

In conclusion, tezepelumab can be considered a cost-effective treatment option for all severe uncontrolled asthma patients despite high dose ICS and an additional controller, who have experienced 3 or more exacerbations in the prior year, or who receive mOCS, irrespective of biomarkers.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: PATHWAY additional information

Appendix M: NAVIGATOR additional information

Appendix N: SOURCE additional information

Appendix O: Mortality life table model inputs

Appendix P: Model input parameters

Appendix Q: Full definition of non-bio eligible (3+ exacs OR mOCS) patient subgroup

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.


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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]				

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

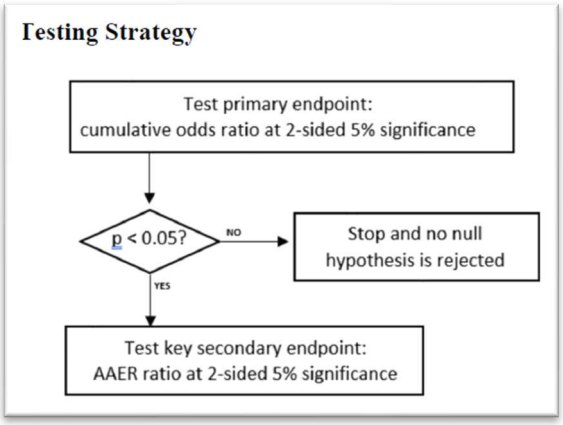
Region	Country	Number (%) of subjects		
		Tezepelumab 210 mg Q4W (N=74)	Placebo (N=76)	Total (N=150)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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.

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% CrI)
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]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[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]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]		[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]	[redacted]
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	[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; 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]									

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]									

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

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

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

[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
15	Meyers, A.	American Journal of Respiratory and Critical Care Medicine. 2017;195(no pagination).	Burden of disease of severe uncontrolled asthma: A european study
16	Muellerova, H.	European Respiratory Journal. Conference: European Respiratory Society Annual Congress.2016;48(no pagination).	Clinical characteristics and burden of illness in a cohort of severe asthma patients
17	Nordon, C.	Value in Health.2016;19 (7):A560-A561.	The burden of severe asthma in France
18	Omarjee, B.	Allergy: European Journal of Allergy and Clinical Immunology.2017;72:643.	Costs of exacerbations in asthma in a French tropical island (Reunion Island)
19	Pedrini, A.	Value in Health.2016;19 (3):A112.	Burden of disease and health care costs of adult patients with severe refractory asthma in a big real-world data base (ARCO)
20	Raimundo, K.	Journal of Allergy and Clinical Immunology.2016;1):AB5.	Cost and healthcare utilization in asthma patients with high oral corticosteroid use
21	Sullivan, P. W.	Journal of Allergy and Clinical Immunology.2014; 1):AB41.	Characterizing the severe asthma population in the United States: Claims-based analysis of three treatment cohorts in the year prior to treatment escalation
22	Tan, L. L.	Proceedings of Singapore Healthcare.2012;21:S87.	Exacerbation-prone severe asthma phenotype in Singapore: Epidemiological and clinical factors

Nr	Author	Citation	Title
23	Tay, T. R.	Annals of the Academy of Medicine, Singapore. 2017;46(6):217-228.	Comparison of the Proportion and Healthcare Utilisation of Adult Patients with Uncontrolled Severe Asthma versus Non-Severe Asthma Seen in a Southeast Asian Hospital-Based Respiratory Specialist Clinic
24	West, L. M.	European Respiratory Journal. 2013;42(no pagination).	Clinical and economic outcomes following 52-week add-on omalizumab
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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NICE National Institute for Health and Care Excellence

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

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NICE National Institute for Health and Care Excellence

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.

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	**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.	

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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
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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]

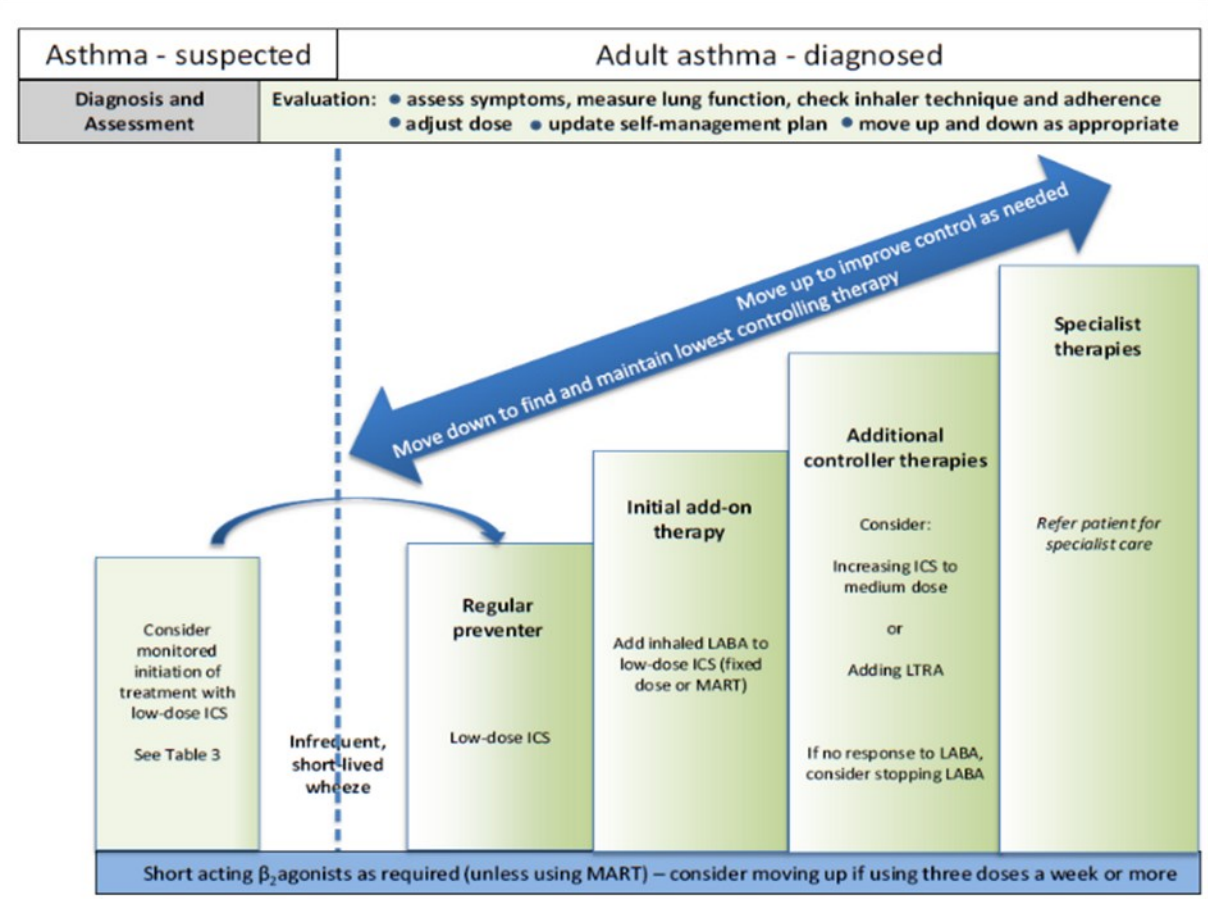
The CS describes the burden of severe, uncontrolled asthma is high due to associated exacerbations and hospitalisations.[12] The unpredictability and distress associated with severe, uncontrolled asthma symptoms has a substantial negative impact on the lives of patients, including a detriment in the 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 <u>Adults and adolescents (12 years of age and older):</u> 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 <u>Children (6 to <12 years of age):</u> 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.

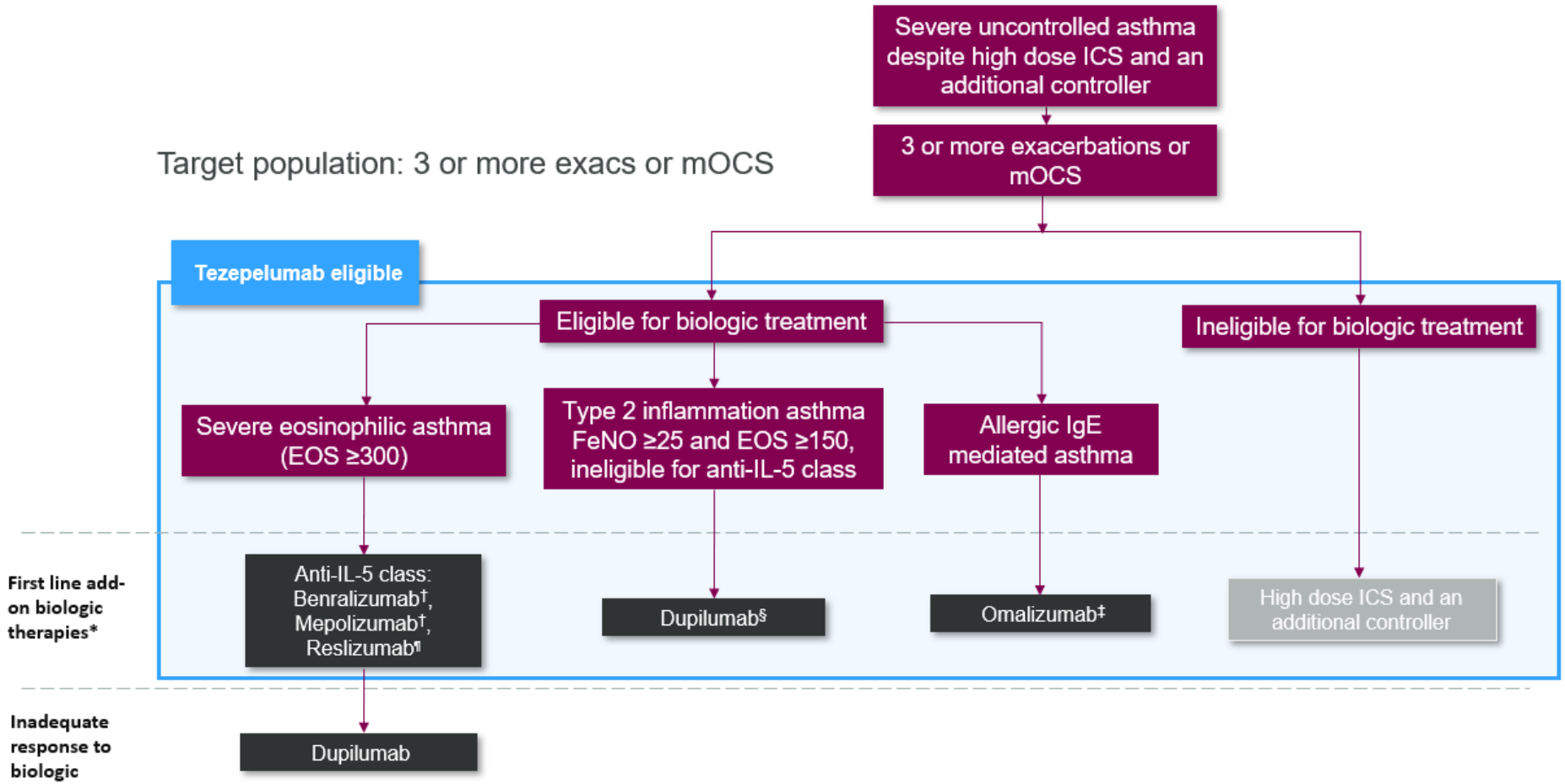
Source: Jackson 2021 [32].

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)

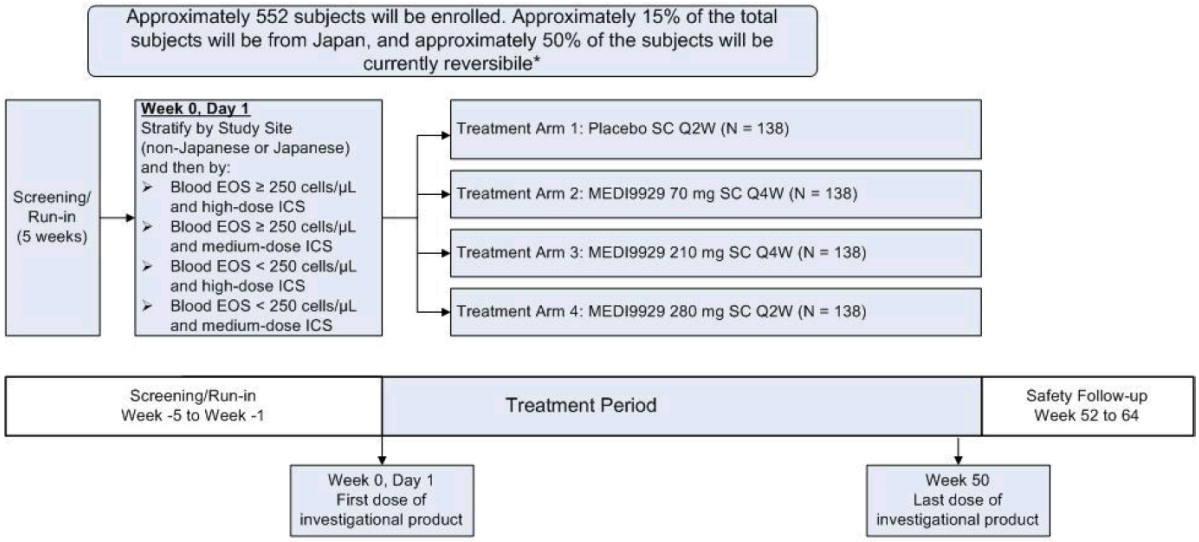
Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; mOCS, maintenance oral corticosteroids; RCT, randomized controlled trial; SC, subcutaneous; SoC, standard of care; Q4W, once every four weeks

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.

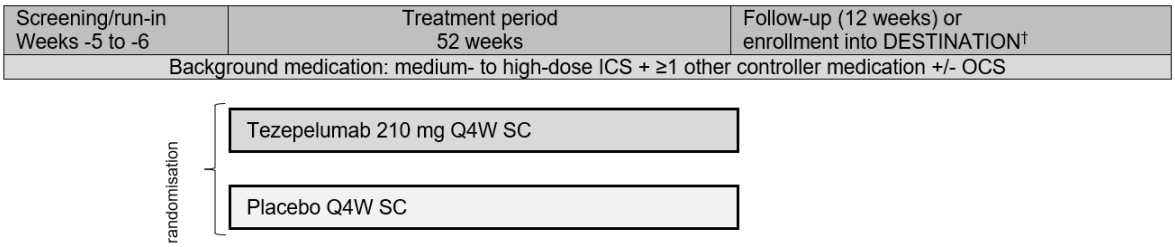
Figure 3: Schematic of PATHWAY trial design



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

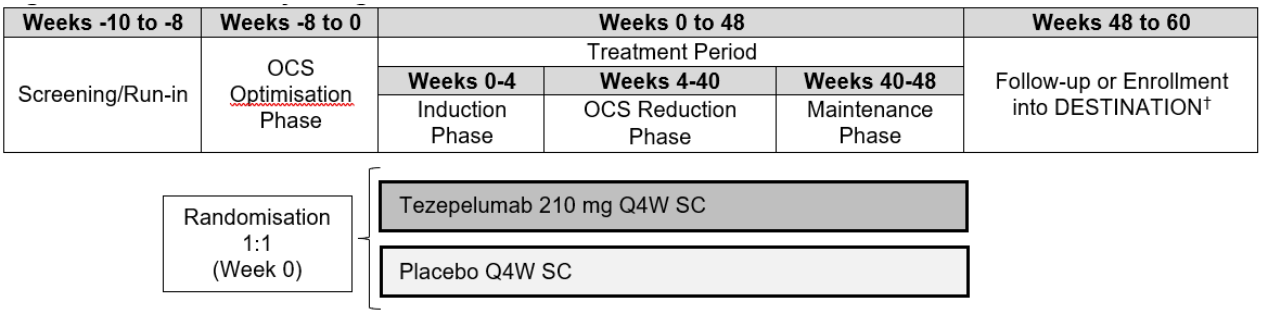
Figure 4: Schematic of NAVIGATOR trial design



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 subgroups*

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.

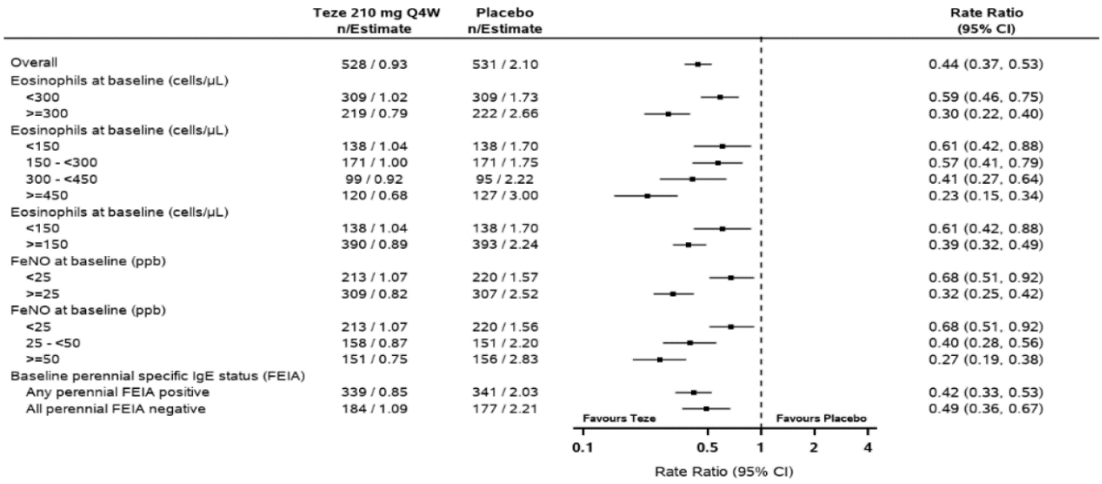
Figure 6: AAER over 52 weeks by pre-planned subgroups (ITT) in PATHWAY

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)



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]										

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]								

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]. 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. 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]										

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]	

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]

[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

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

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

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

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.

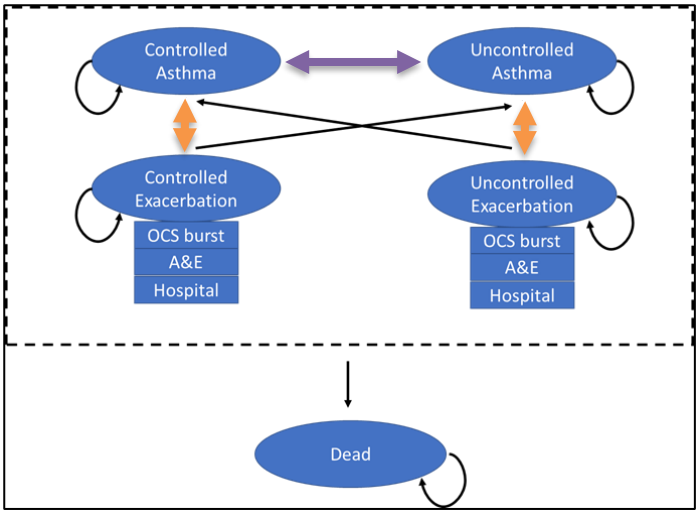
4.2.6. Treatment effectiveness and extrapolation

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

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

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

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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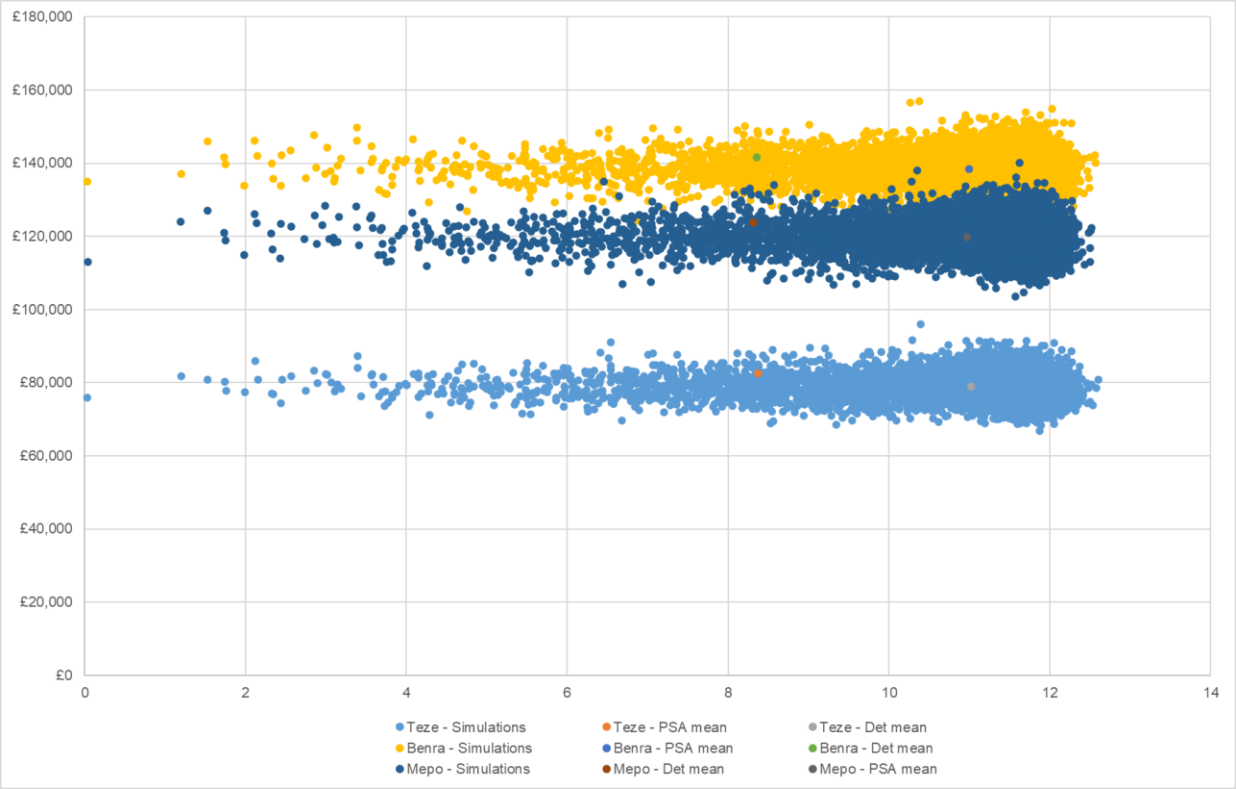
Appendix 1: EAG base case assumptions: CE plane and CE frontier

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.

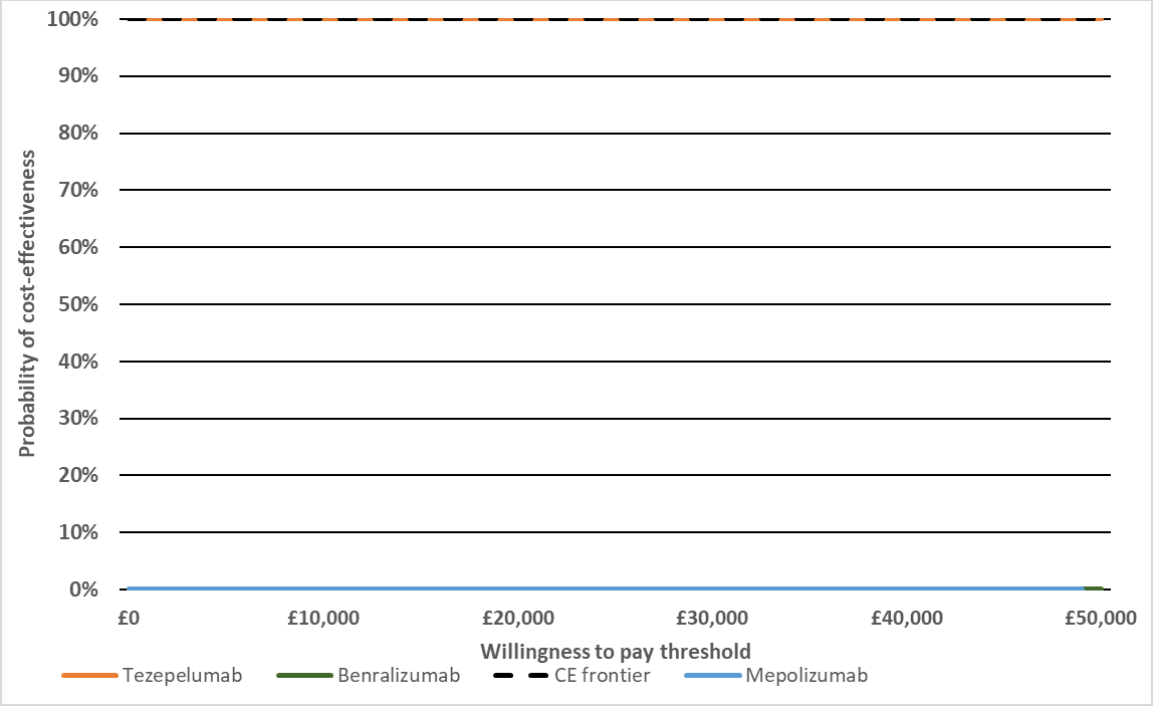
Anti-IL5 eligible subgroup

Figure 13: Incremental cost-effectiveness scatter plot (anti-IL-5 eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; PSA, probabilistic sensitivity analysis.

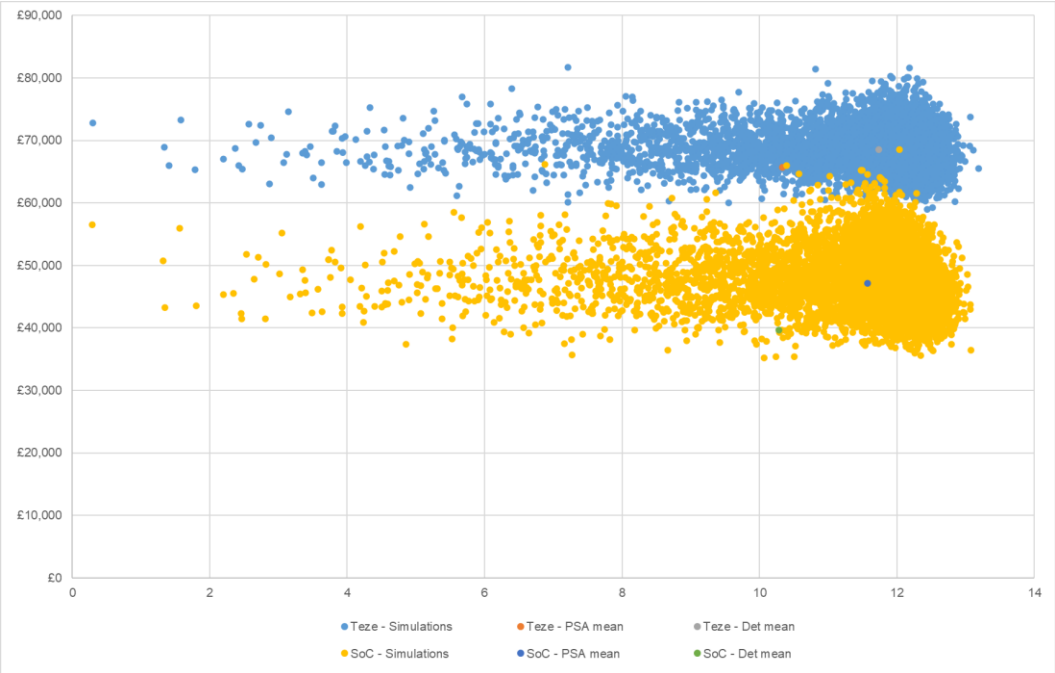
Figure 14: Cost-effectiveness frontier (anti-IL-5 eligible)



Abbreviations: CE, cost-effectiveness; IL, interleukin.

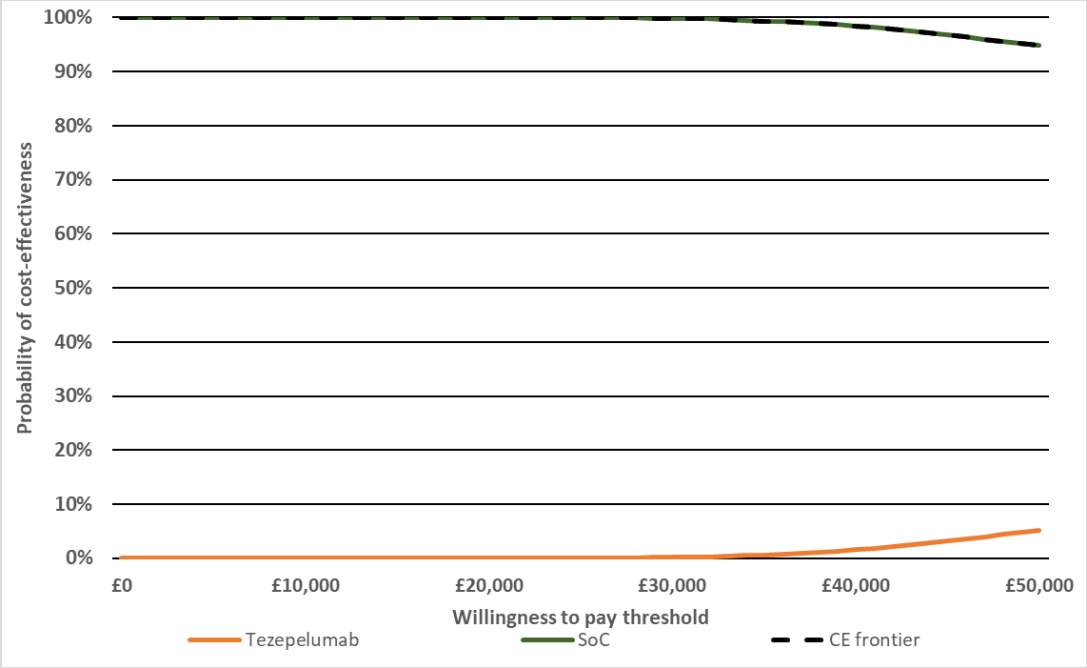
Non-bio eligible subgroup

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.

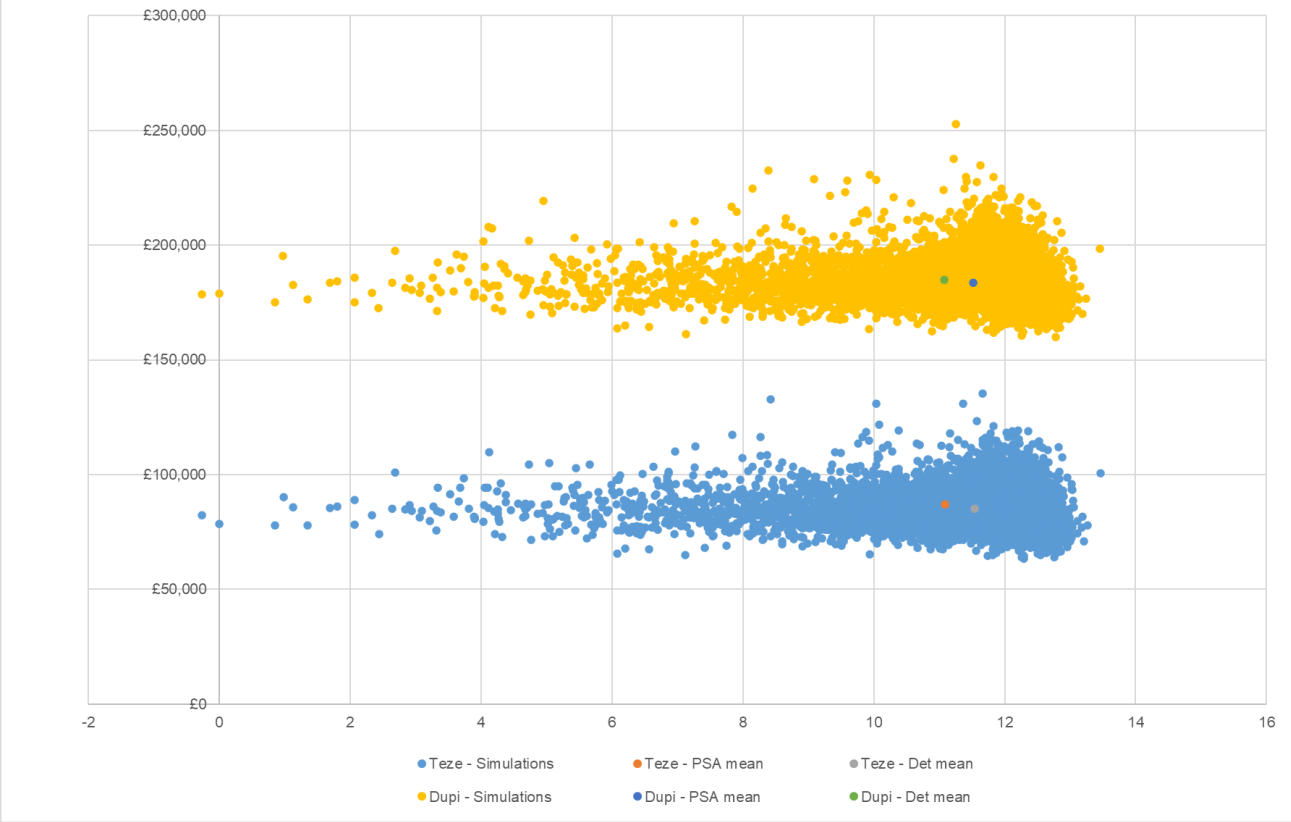
Figure 16: Cost-effectiveness frontier (non-bio eligible [3+ exacs OR mOCS])



Abbreviations: CE, cost-effectiveness; exacs, exacerbations; mOCS, maintenance oral corticosteroid treatment; SoC, standard of care.

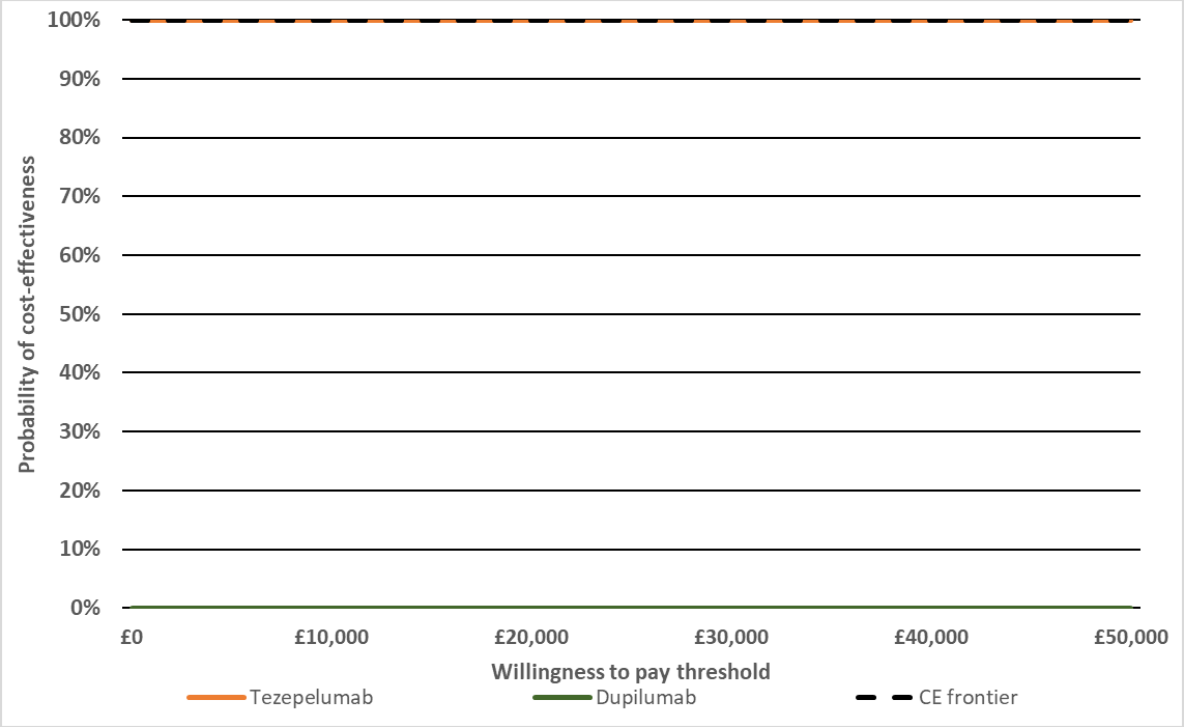
Dupilumab-eligible subgroup

Figure 17: Incremental cost-effectiveness scatter plot (dupilumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

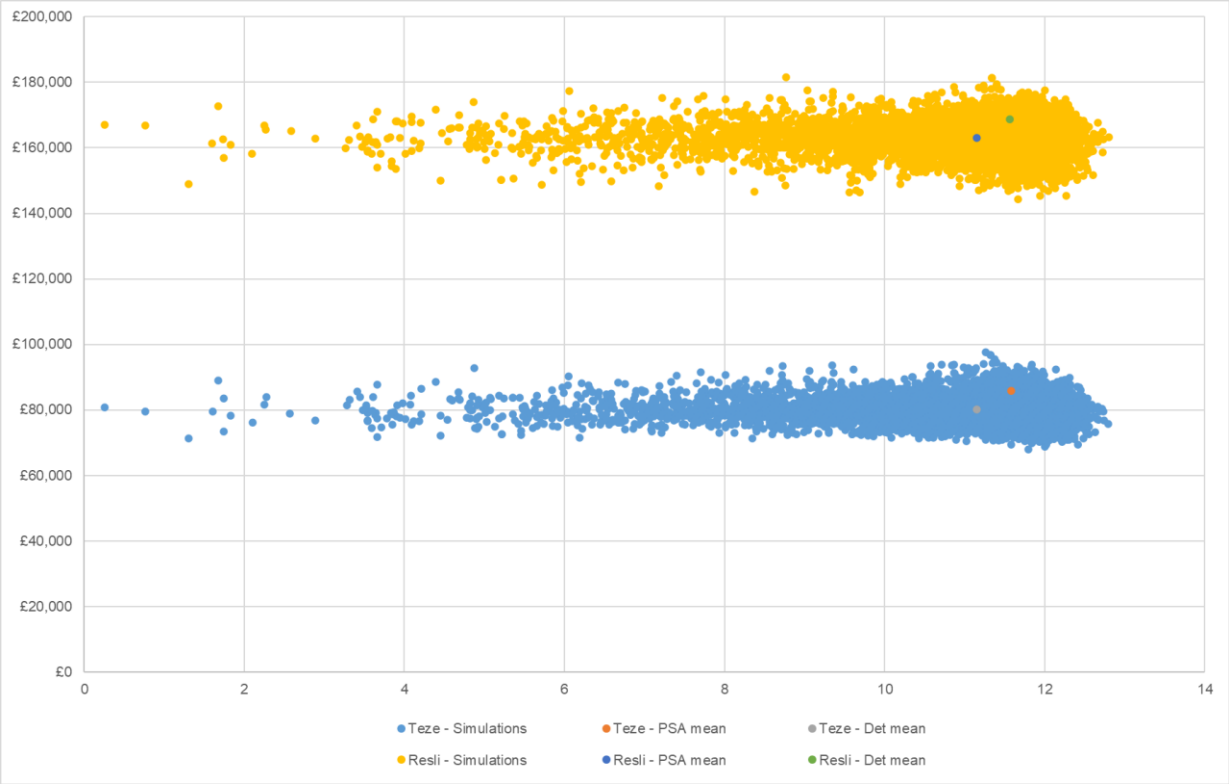
Figure 18: Cost-effectiveness frontier (dupilumab eligible)



Abbreviations: CE, cost-effectiveness.

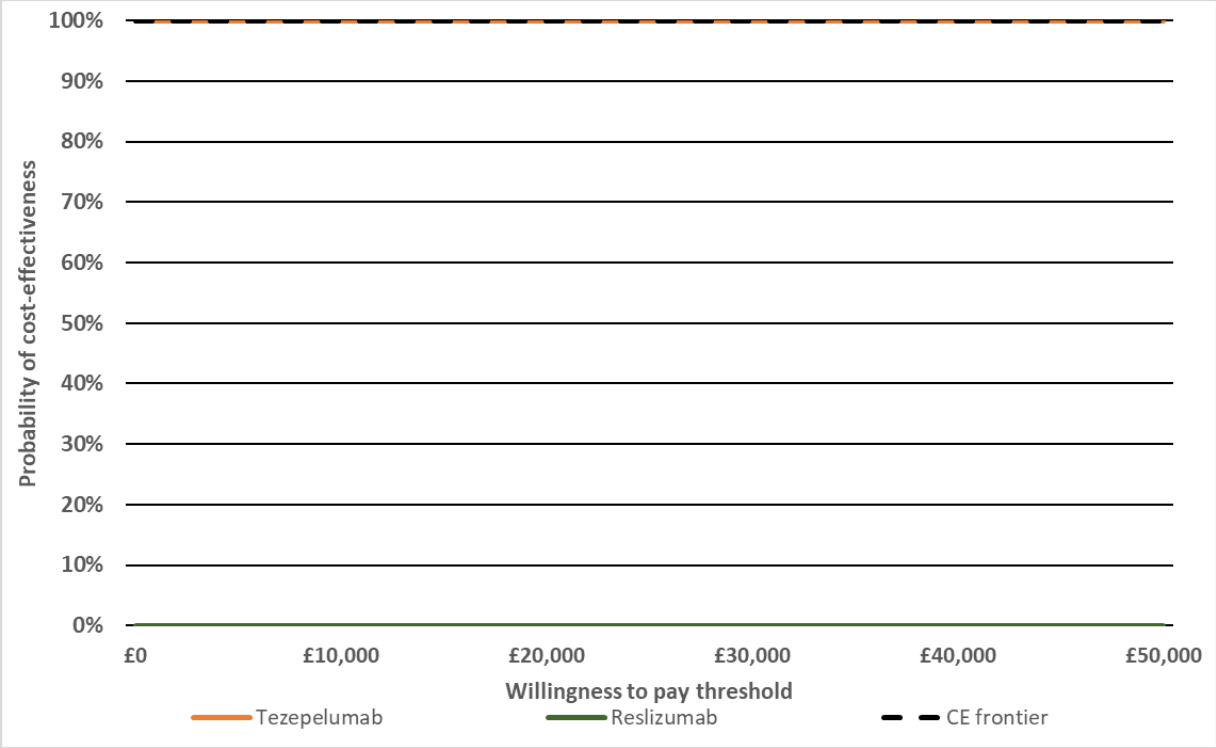
Reslizumab-eligible subgroup

Figure 19: Incremental cost-effectiveness scatter plot (reslizumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

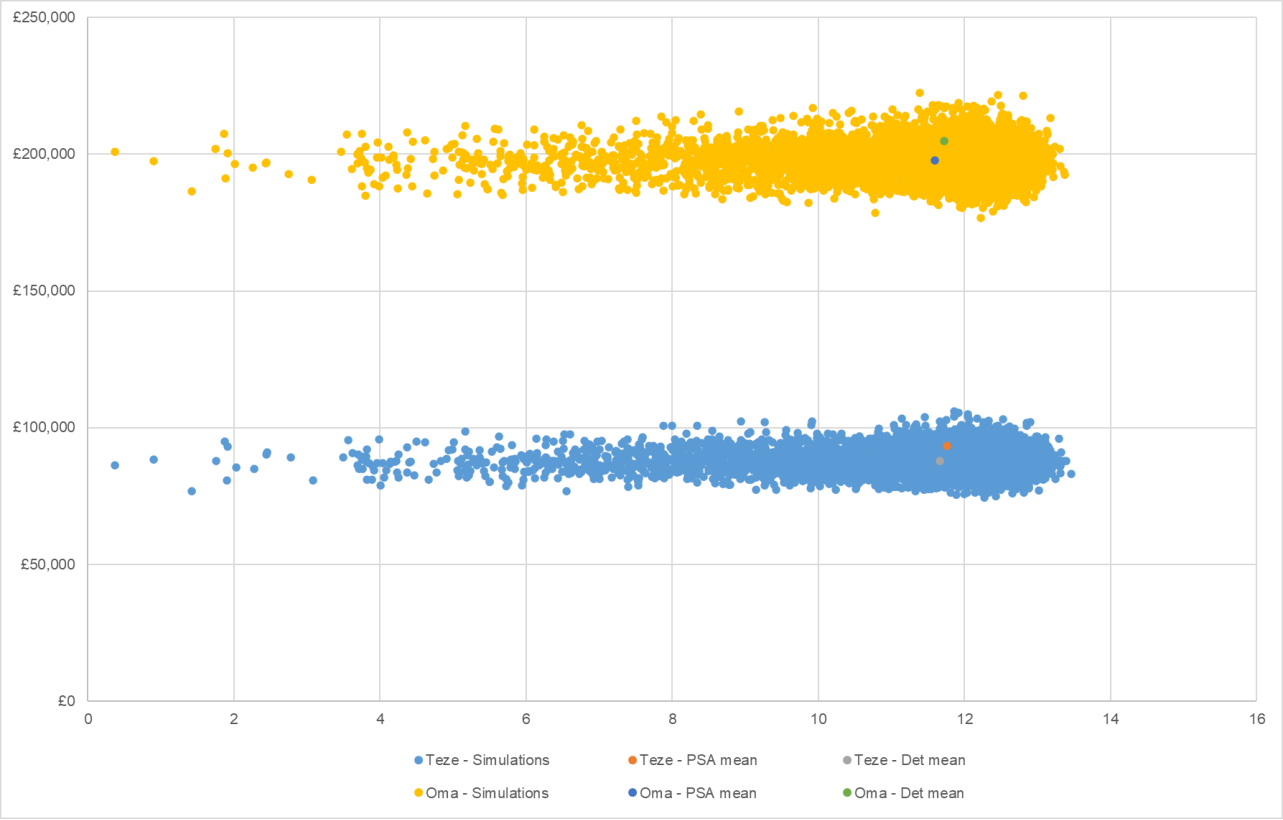
Figure 20: Cost-effectiveness frontier (reslizumab eligible)



Abbreviations: CE, cost-effectiveness.

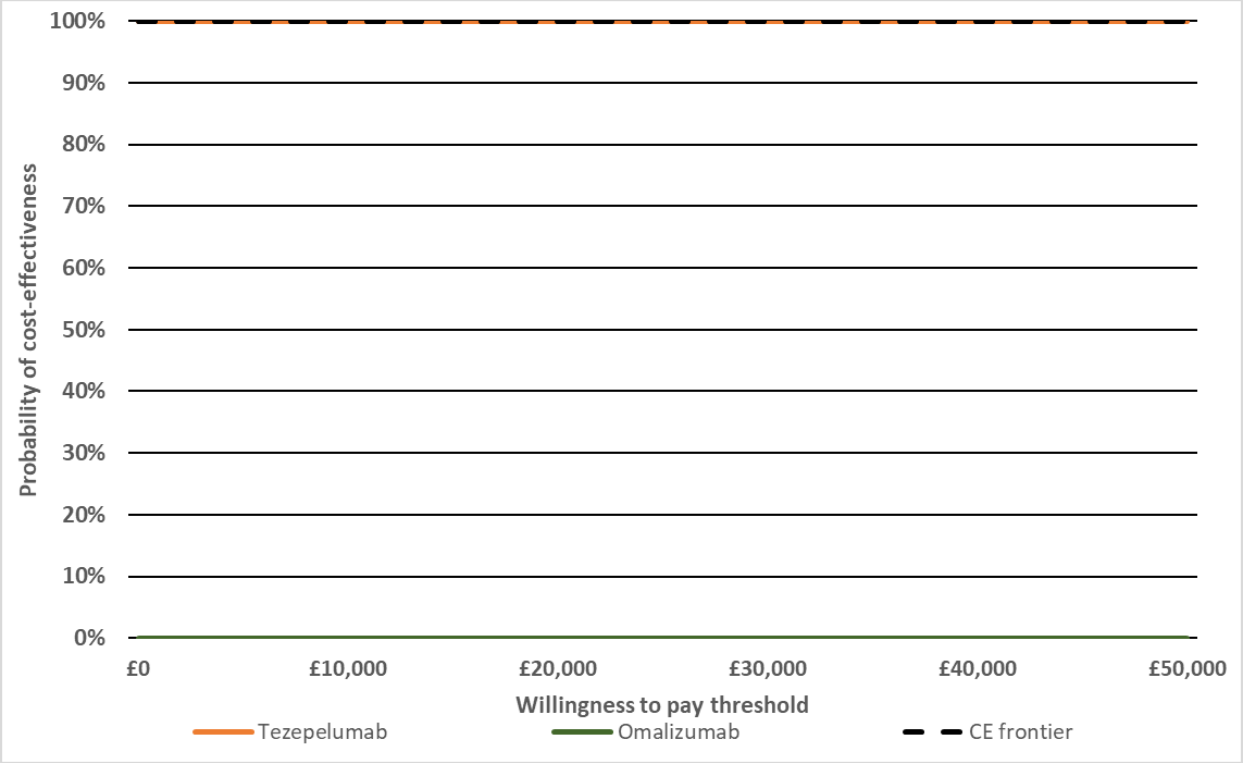
Omalizumab-eligible subgroup

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.

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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.

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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.

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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	<u>The company's approach, as best as possible, aligns with NICE's recommendations for severe asthma biologics</u> 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.

		<u>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</u> 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. <u>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</u> 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	<u>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</u> 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. 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 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]

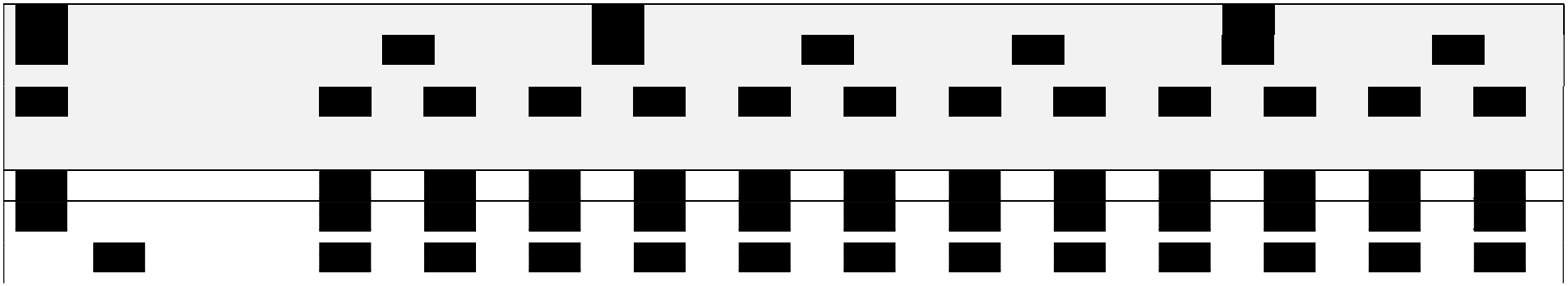
Table 3: Summary of on-treatment adverse events from DESTINATION

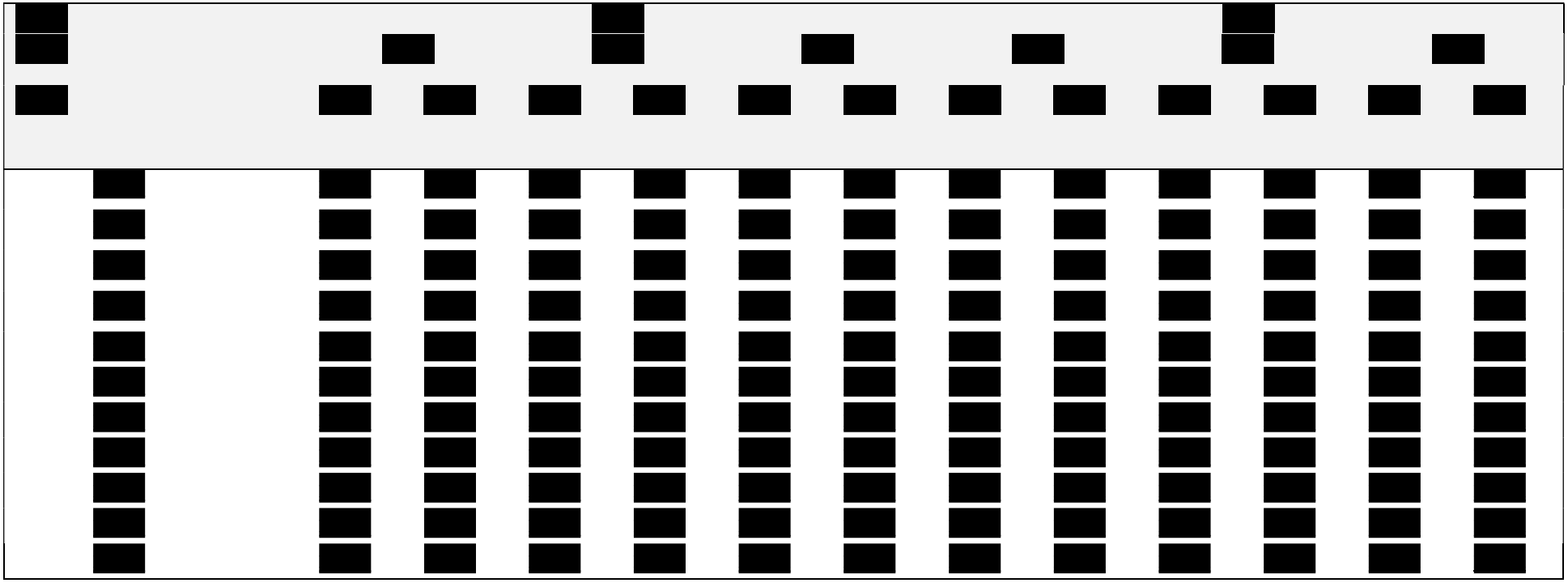
Parent study	NAVIGATOR		SOURCE	
	'Rand teze' (n=528)	'Rand pbo' (n=531)	'Rand teze' (n=74)	'Rand pbo' (n=76)
Total time at risk across all patients (years)	917·0	699·0	129·4	100·0
Any AE				
n (%)	455 (86·2)	438 (82·5)	61 (82·4)	70 (92·1)
Incidence (per 100 patient-years)	49·62	62·66	47·15	69·97
Any 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





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

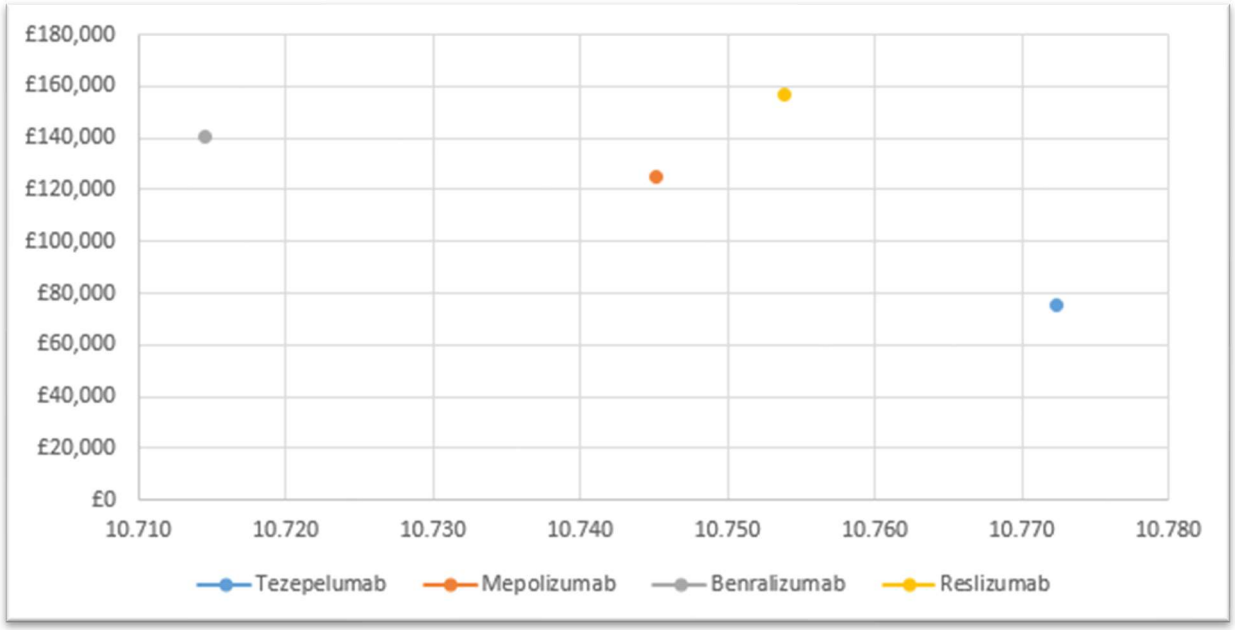
Table 16: Base case results (reslizumab eligible)

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)

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)

Abbreviations: CE, cost-effectiveness; IL, interleukin.

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NICE National Institute for Health and Care Excellence

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.

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NICE National Institute for Health and Care Excellence

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

[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)

[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).

[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?	<u>Oral corticosteroids (OCS)</u> 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]

[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."*

[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

[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

[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.

[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.

[22] Asthma UK, https://www.asthma.org.uk/advice/inhalers-medicines-treatments/steroids/ (accessed 12/02/2019)

Thank you for your time.

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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

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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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