Tezepelumab for treating severe asthma [ID3910]

A Single Technology Appraisal

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

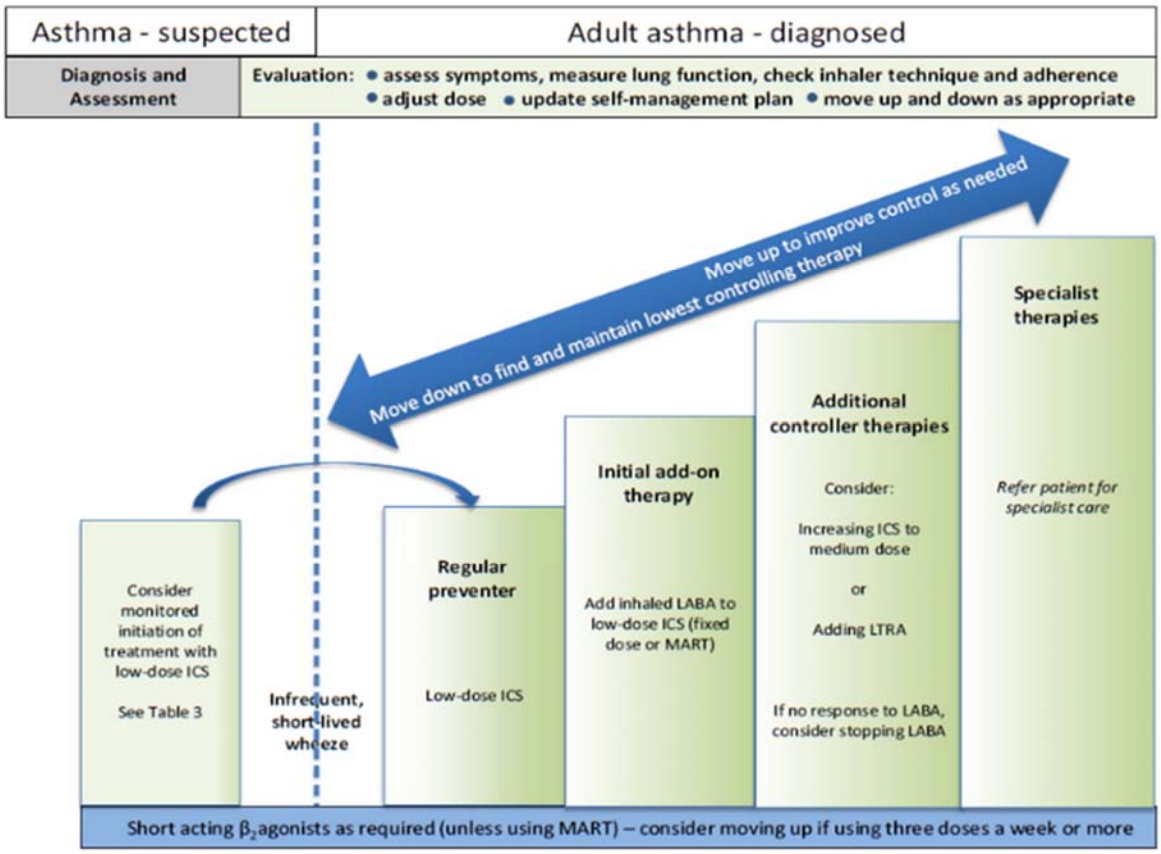
The CS describes the burden of severe, uncontrolled asthma is high due to associated exacerbations and hospitalisations.[12] The unpredictability and distress associated with severe, uncontrolled asthma symptoms has a substantial negative impact on the lives of patients, including a detriment in the 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)

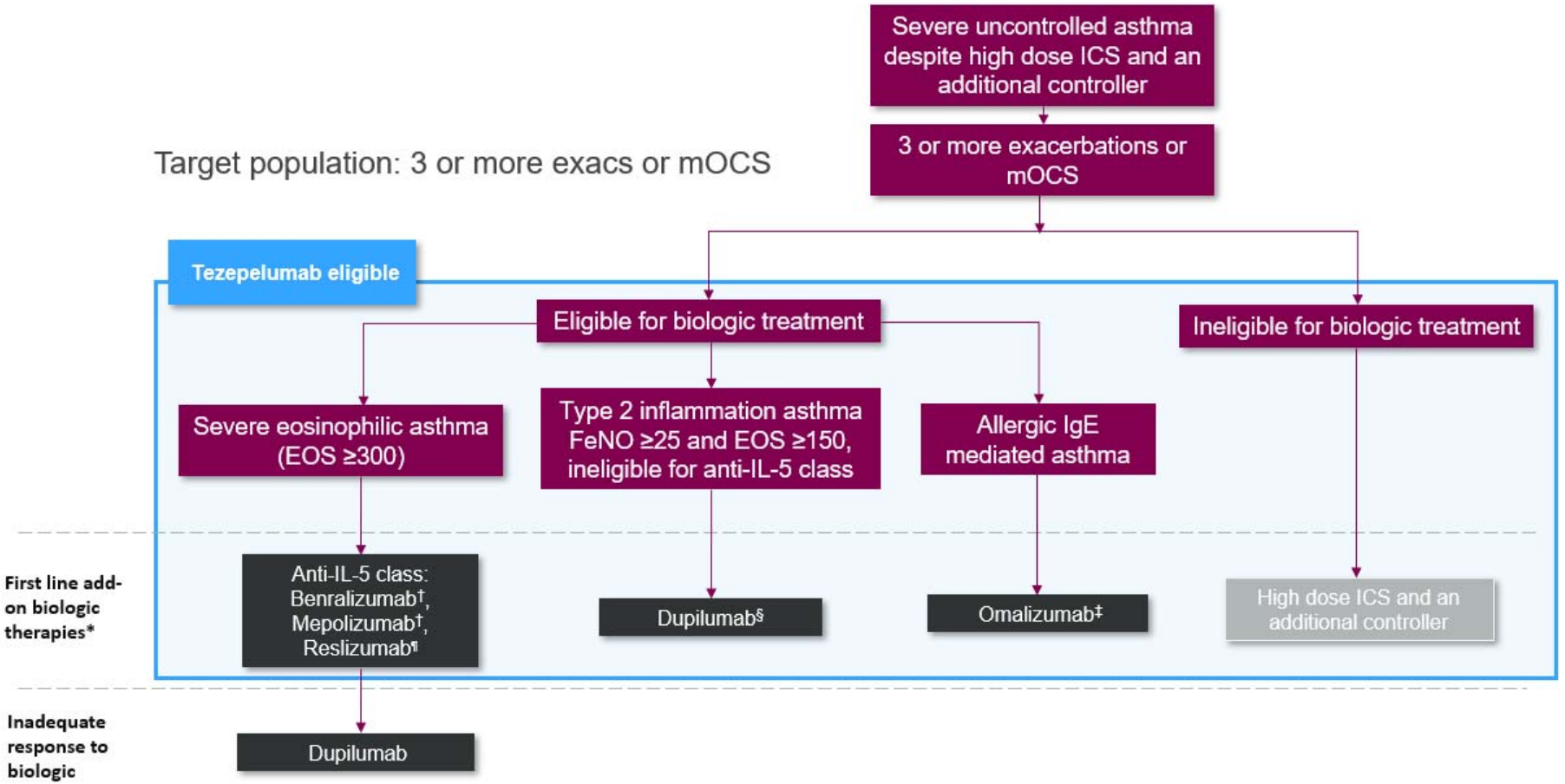
Abbreviations: UKSAR, UK Severe Asthma Registry.
Source: Jackson 2021 [32].

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)

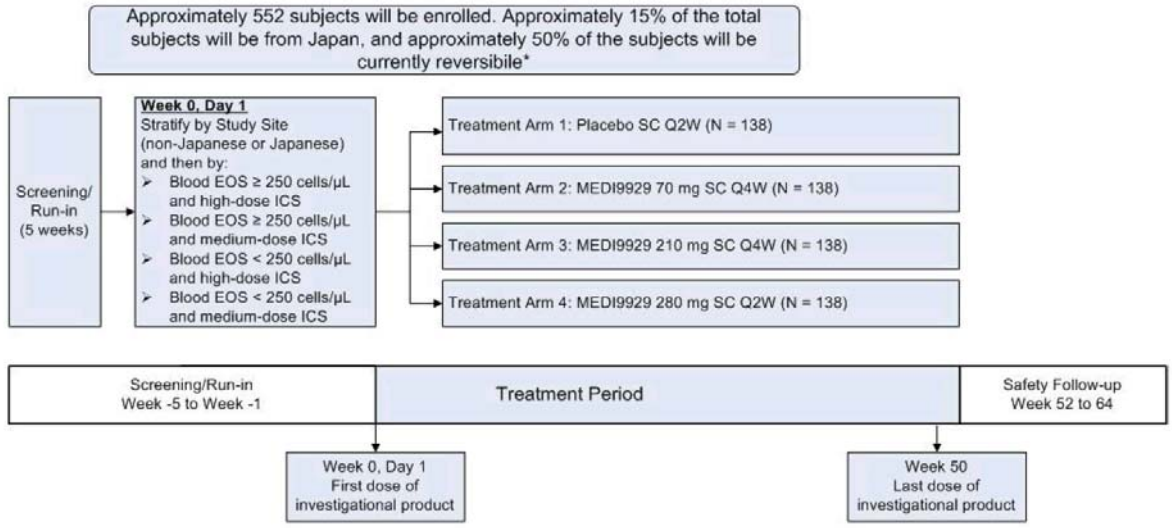
Abbreviations: ACQ-6, Asthma Control Questionnaire 6-item; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; mOCS, maintenance oral corticosteroids; RCT, randomized controlled trial; SC, subcutaneous; SoC, standard of care; Q4W, once every four weeks

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.

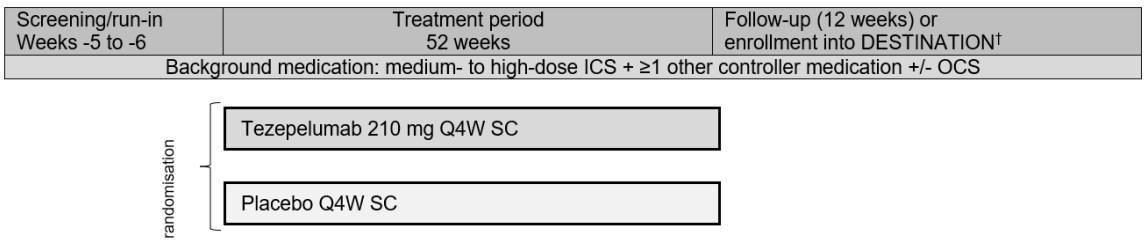
Figure 3: Schematic of PATHWAY trial design



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

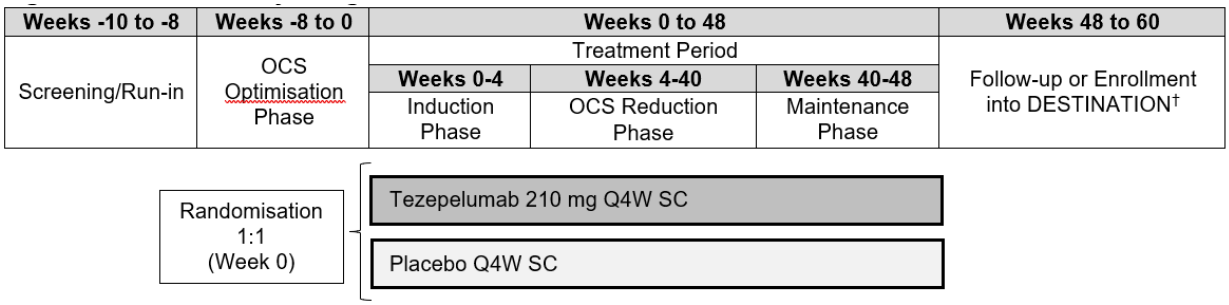
Figure 4: Schematic of NAVIGATOR trial design



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 sub*groups**

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

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

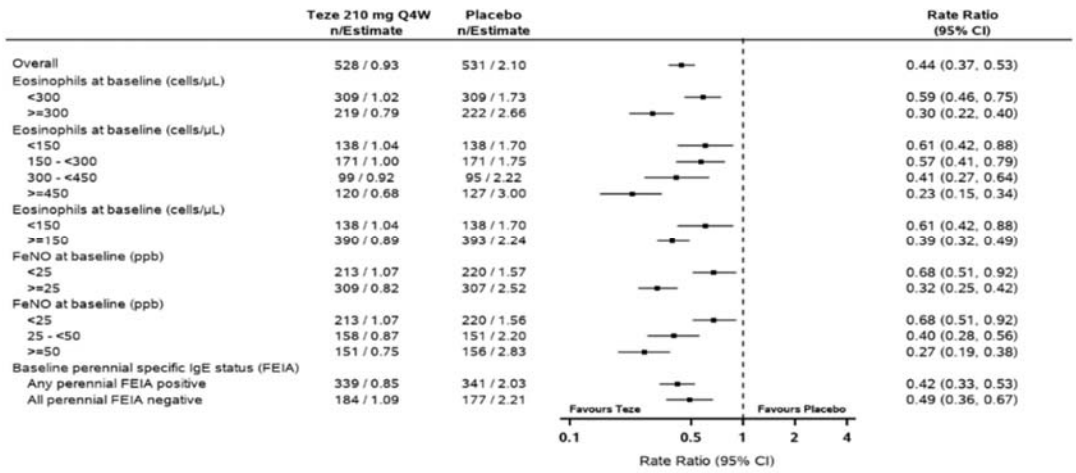
[redacted]

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

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

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

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



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]						

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

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

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

Daily asthma symptom diary

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

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

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

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

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

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

timeframe the data were collected at baseline and the study endpoint. Similar data were not available for PATHWAY.

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

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

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

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

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

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

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

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

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

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

Table 21: CFB to Week 52 in pre-BD FEV_1: NAVIGATOR post-hoc subgroups

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

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

Table 22: CFB to Week 48 in pre-BD FEV_1: SOURCE post-hoc subgroups

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

Abbreviations: BD, bronchodilator; CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in the first second; LS, least squares; MMRM, mixed-effects model for repeated measures; mOCS, maintenance oral corticosteroid treatment; SE, standard error. Baseline is defined as the last non-missing measurement recorded on or prior to randomisation. Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + baseline FEV1 + visit + treatment * visit. Subjects with data at baseline and at least at one post-baseline time point included in analysis. Source: Adapted from Tables 70, 74, 78 and 82, CS, Document B, Section B.2.7.2.2.

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

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

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

Health-related quality of life

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

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

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

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

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

[redacted]

EQ-5D-5L visual analogue scale (VAS) scores were also reported for all three key tezepelumab studies. For PATHWAY it was stated in CS L.2.10 that [redacted] However, no accompanying data were provided. For NAVIGATOR, CS, Document B, Section B.2.6.2.6 Table 41 reported [redacted] For SOURCE, CS, Document B, Section B.2.6.3.3 Table 47 reported that, over 48 weeks, and compared with placebo, those treated with tezepelumab had a greater improvement in EQ-5D-5L visual analogue scale scores (LS mean difference 7.21, 95% CI 1.01, 13.41, p<0.023). It was also stated that, in NAVIGATOR,

tezepelumab improved scores and increased the [redacted] at 52 weeks compared with placebo, but accompanying data were not provided.

Adverse effects

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

AEs and SAEs

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

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

Treatment-related AEs and SAEs

Treatment-related AEs (TRAEs) were also found at similar rates for participants in the tezepelumab 210 mg Q4W and placebo arms of the three key studies. For PATHWAY, these

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

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

Discontinuations

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

Deaths

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

Commonly reported AEs

The most frequently reported AEs in PATHWAY, occurring in at least 5% of participants, were asthma, nasopharyngitis, bronchitis, and headache (Table 25), with the latter three conditions occurring at similar frequencies in the tezeplemab 210 mg Q4W and placebo arms (asthma

occurred at a greater frequency in the placebo arm). In NAVIGATOR, [redacted] were the most frequently reported AEs (Table 26), and with the exception of [redacted], these were reported at similar frequencies in the two study arms. In SOURCE, the most frequently reported adverse events were [redacted] in the tezepelumab arm and [redacted] (Table 27). [redacted] but there is also more uncertainty in this study due to the smaller sample sizes. The Company note that incidence of treatment-emergent anti-drug antibodies was low [redacted] and that [redacted]

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

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

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

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

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

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

Abbreviations: AE, adverse event.
† Sorted by decreasing frequency for preferred term in subjects treated with tezepelumab.
Subjects with multiple events in the same preferred term were counted only once in that preferred term. Subjects with events in more than one preferred term were counted once in each of those preferred terms. Source: CS Table 92, B.2.10.1

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

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

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.

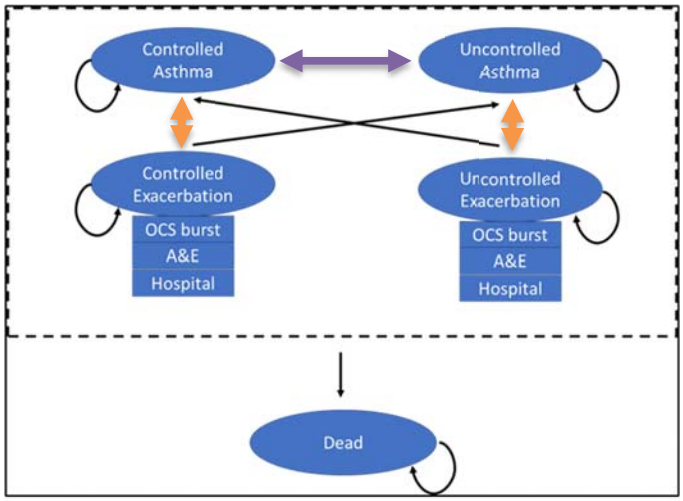
4.2.6. Treatment effectiveness and extrapolation

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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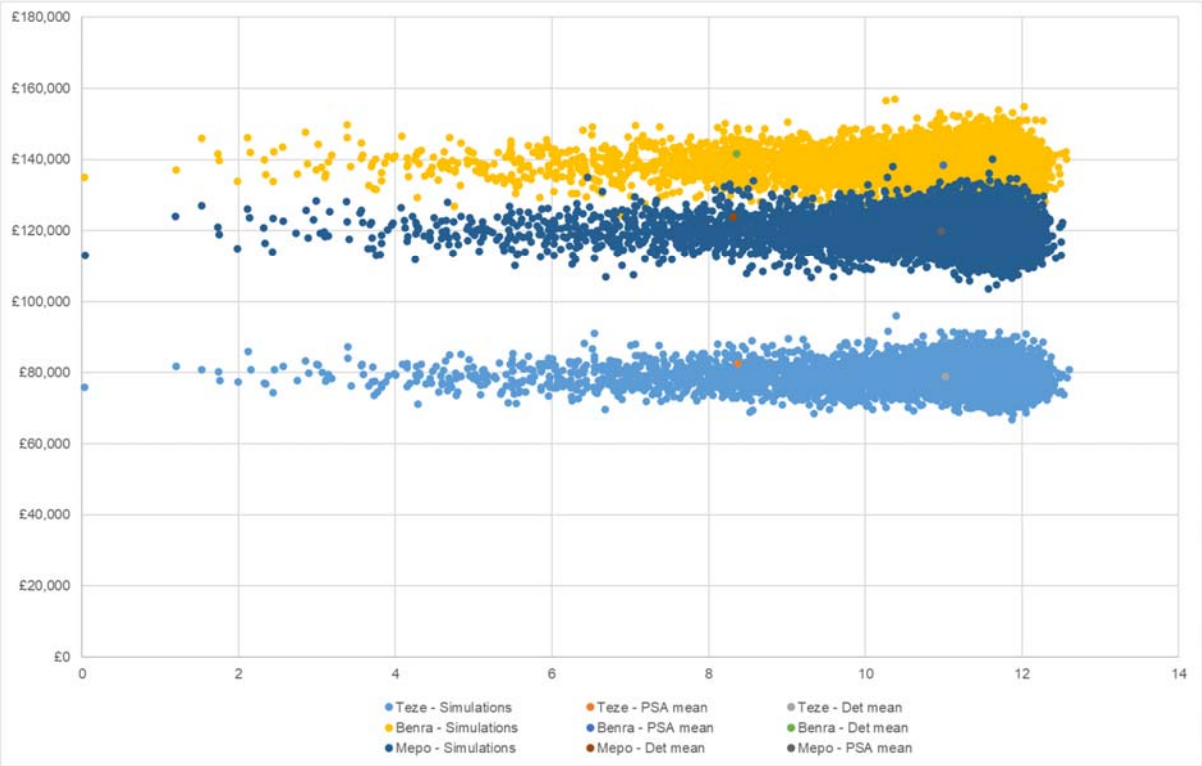
Appendix 1: EAG base case assumptions: CE plane and CE frontier

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.

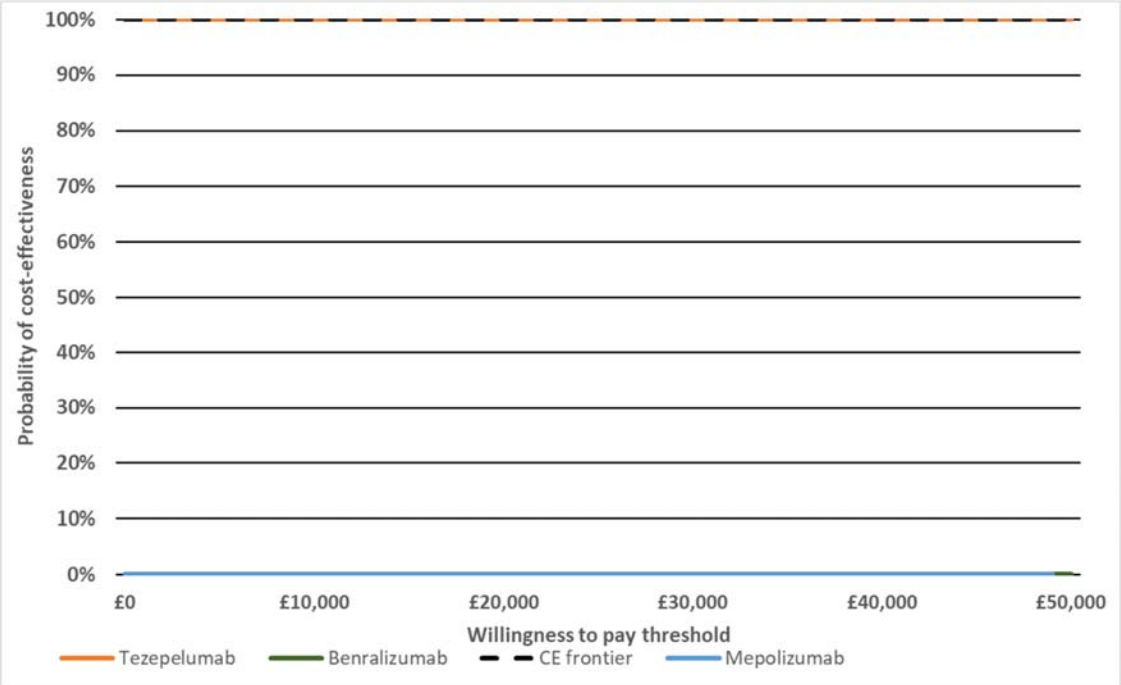
Anti-IL5 eligible subgroup

Figure 13: Incremental cost-effectiveness scatter plot (anti-IL-5 eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; IL, interleukin; PSA, probabilistic sensitivity analysis.

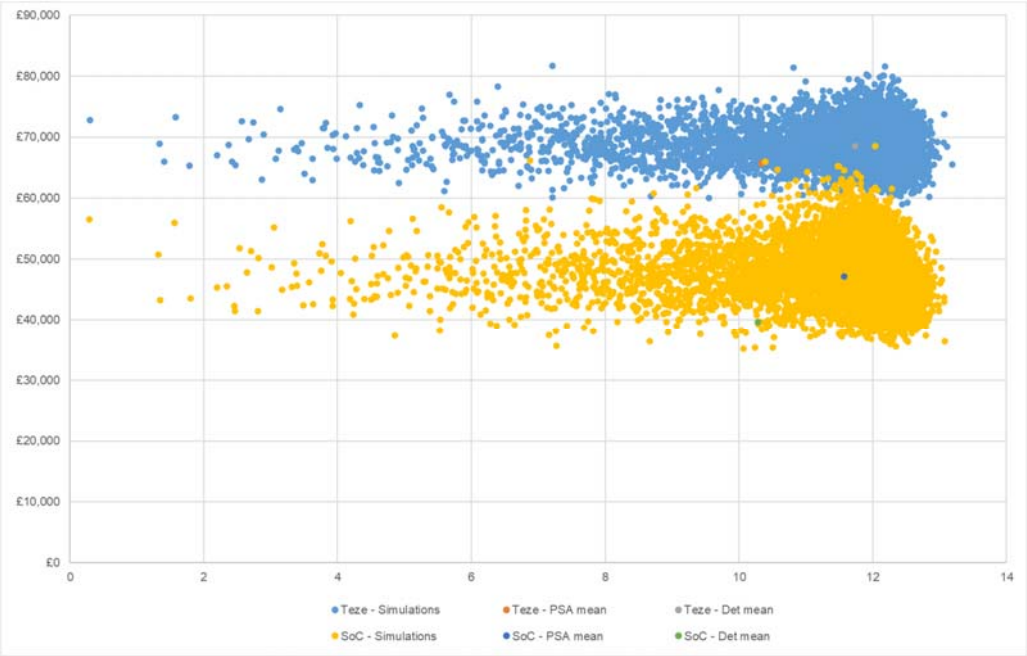
Figure 14: Cost-effectiveness frontier (anti-IL-5 eligible)



Abbreviations: CE, cost-effectiveness; IL, interleukin.

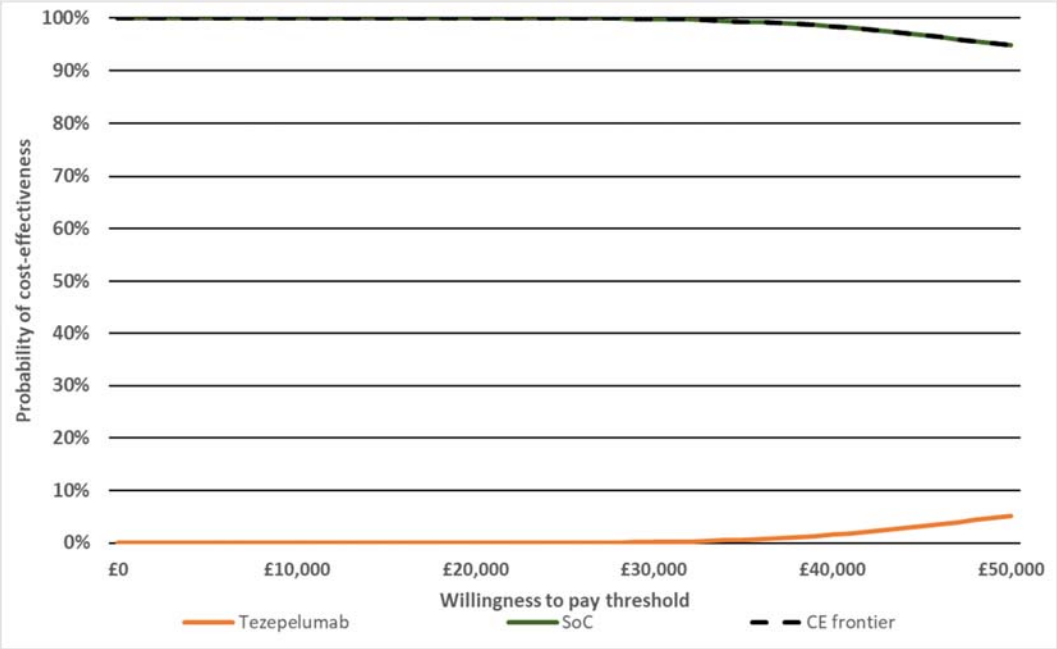
Non-bio eligible subgroup

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.

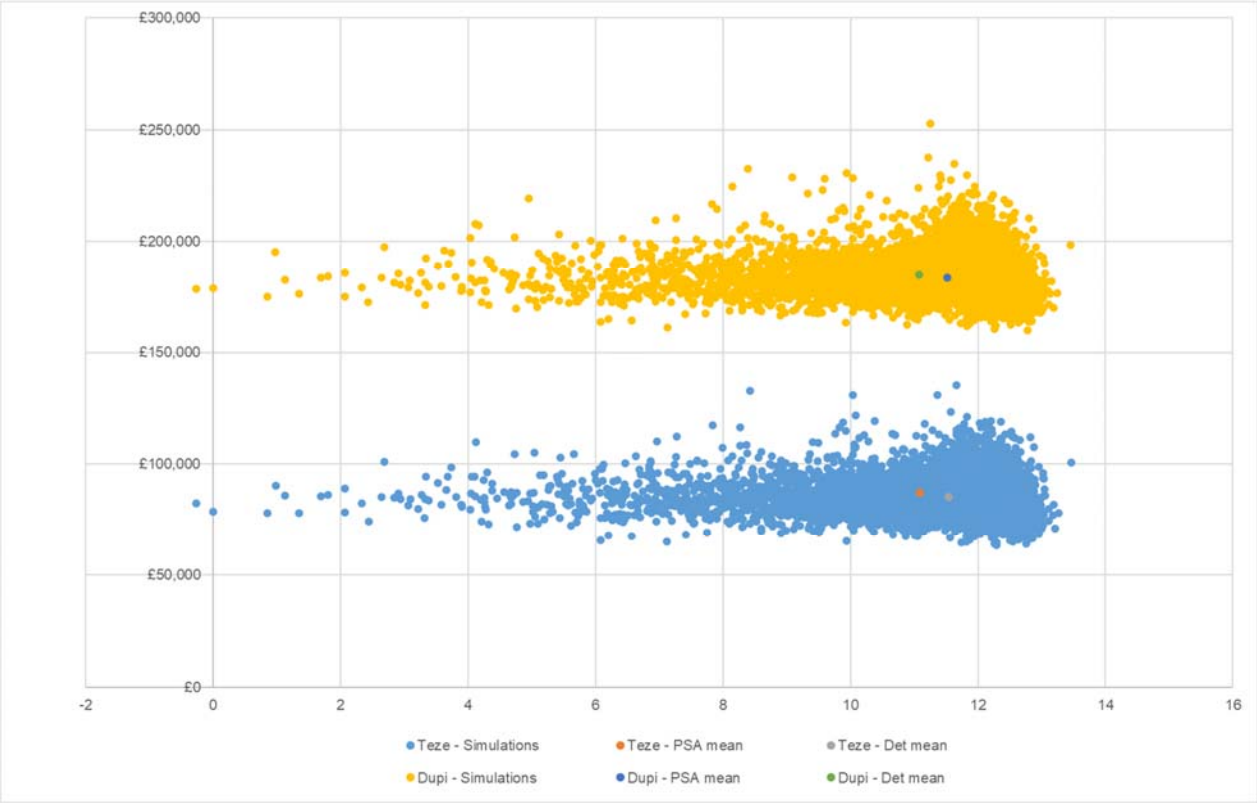
Figure 16: Cost-effectiveness frontier (non-bio eligible [3+ exacs OR mOCS])



Abbreviations: CE, cost-effectiveness; exacs, exacerbations; mOCS, maintenance oral corticosteroid treatment; SoC, standard of care.

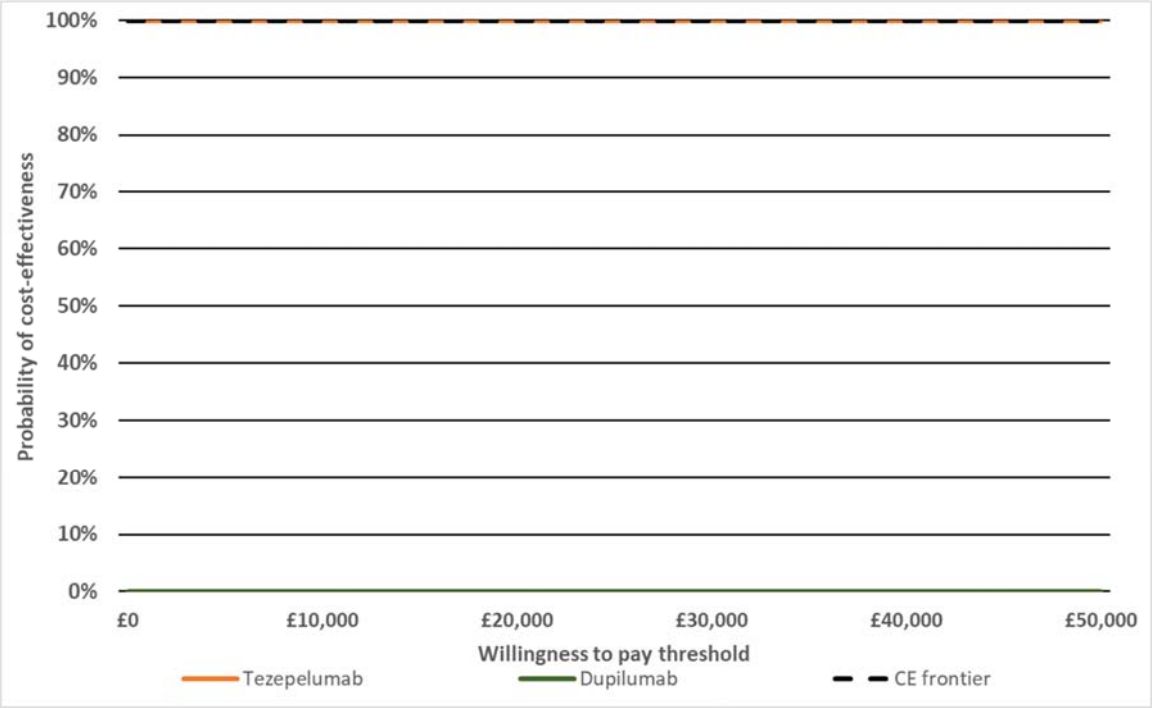
Dupilumab-eligible subgroup

Figure 17: Incremental cost-effectiveness scatter plot (dupilumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

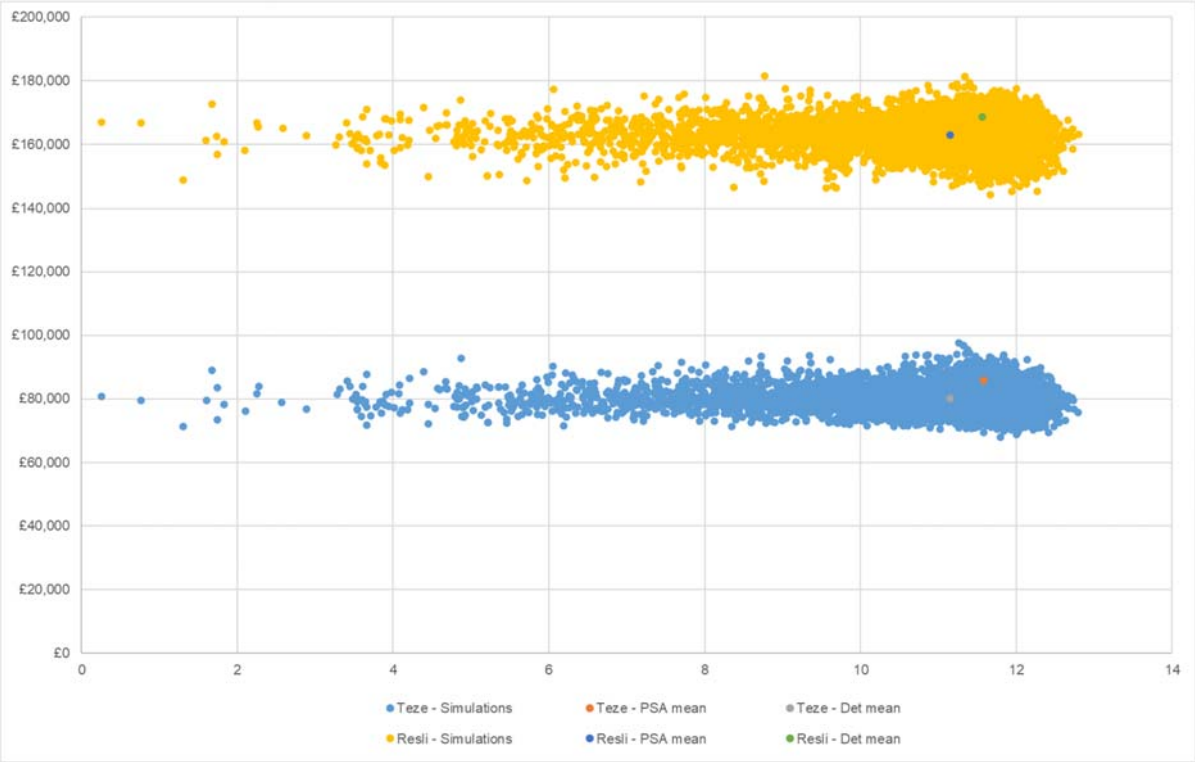
Figure 18: Cost-effectiveness frontier (dupilumab eligible)



Abbreviations: CE, cost-effectiveness.

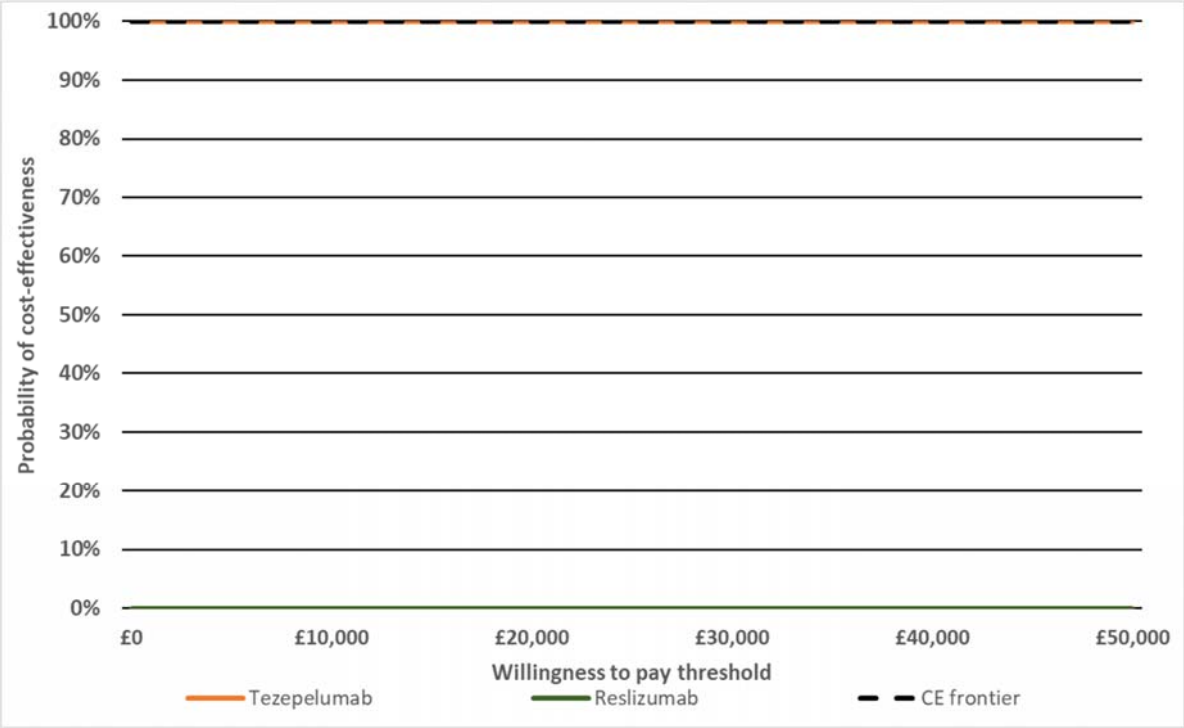
Reslizumab-eligible subgroup

Figure 19: Incremental cost-effectiveness scatter plot (reslizumab eligible)



Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

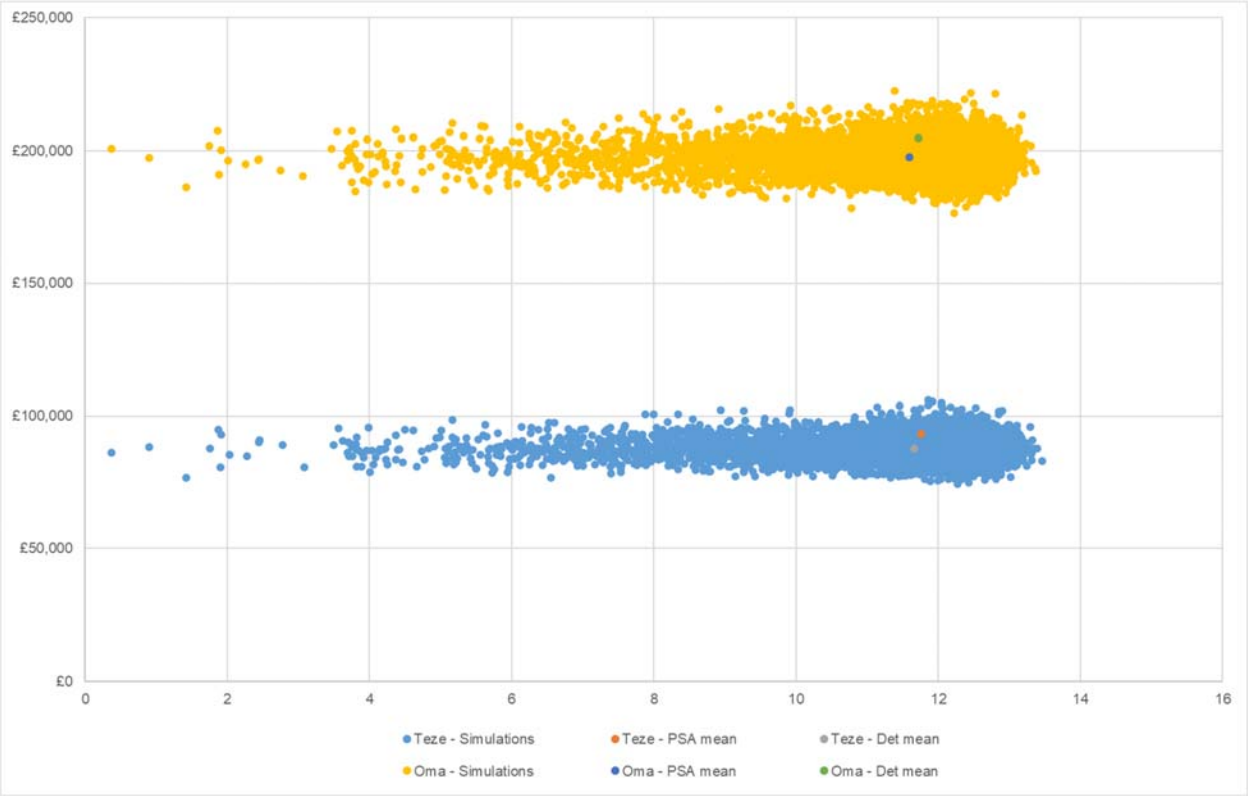
Figure 20: Cost-effectiveness frontier (reslizumab eligible)



Abbreviations: CE, cost-effectiveness.

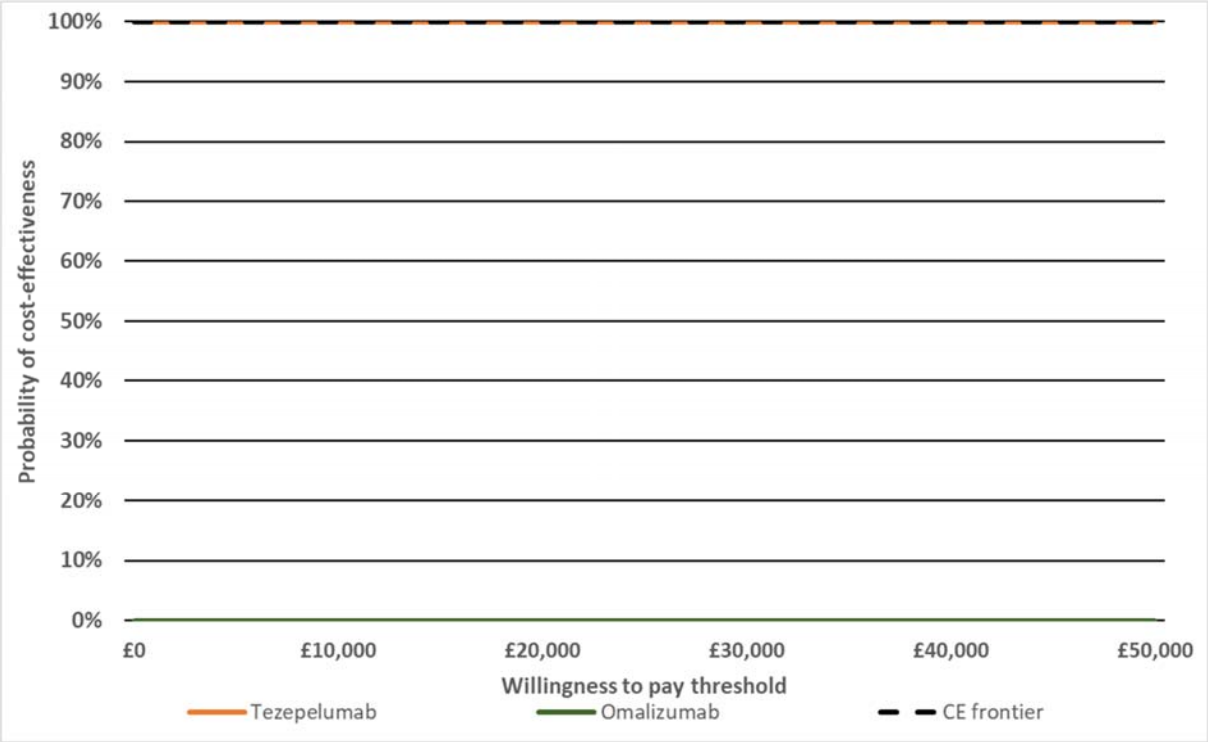
Omalizumab-eligible subgroup

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.