Tezepelumab for treating severe asthma [ID3910]

Part 1– Slides for screen
Contains AIC information

Technology appraisal committee A

[07th February 2023- 2nd meeting]

Chair: Radha Todd

Presenter: James Fotheringham

Evidence review group: PenTAG

Technical team: Harsimran Sarpal, Victoria Kelly, Yelan Guo, Richard Diaz

Company: AstraZeneca

NICE

RECAP

Background: Severe asthma

High unmet need and current treatments are biomarker specific

Severe, uncontrolled asthma: defined as asthma that requires high dose inhaled corticosteroids (ICS) in combination with a long acting beta-agonist (ICS-LABA) to prevent it from becoming uncontrolled, or that remains uncontrolled despite optimised treatment with high dose long acting beta-agonist (ICS-LABA) (GINA 2022, ERS/ATS 2014)

Symptoms and prognosis

- Wheezing, shortness of breath, chest tightness and cough which vary over time and in intensity
- Prognosis based on established phenotype and biomarker profile (including IgE; blood and sputum EOS; FeNOs)

Treatments options

- Standard treatment: inhaled corticosteroids in combination with LABA, with or without LTRAs
- Add-on biological therapies which are biomarker specific: omalizumab (TA278), reslizumab (TA479), benralizumab (TA565), mepolizumab (TA671) and dupilumab (TA751)

Appraisal Consultation Document (ACD):

- Living with severe asthma is physically and emotionally challenging and there is unmet need because some people cannot have existing treatments due to their biomarker profile
- New treatment option without the need for biomarker assessment would be welcome

NICE

Abbreviations: ATS, Asthma Thoracic Society; EOS, eosinophils; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist

Treatment pathway

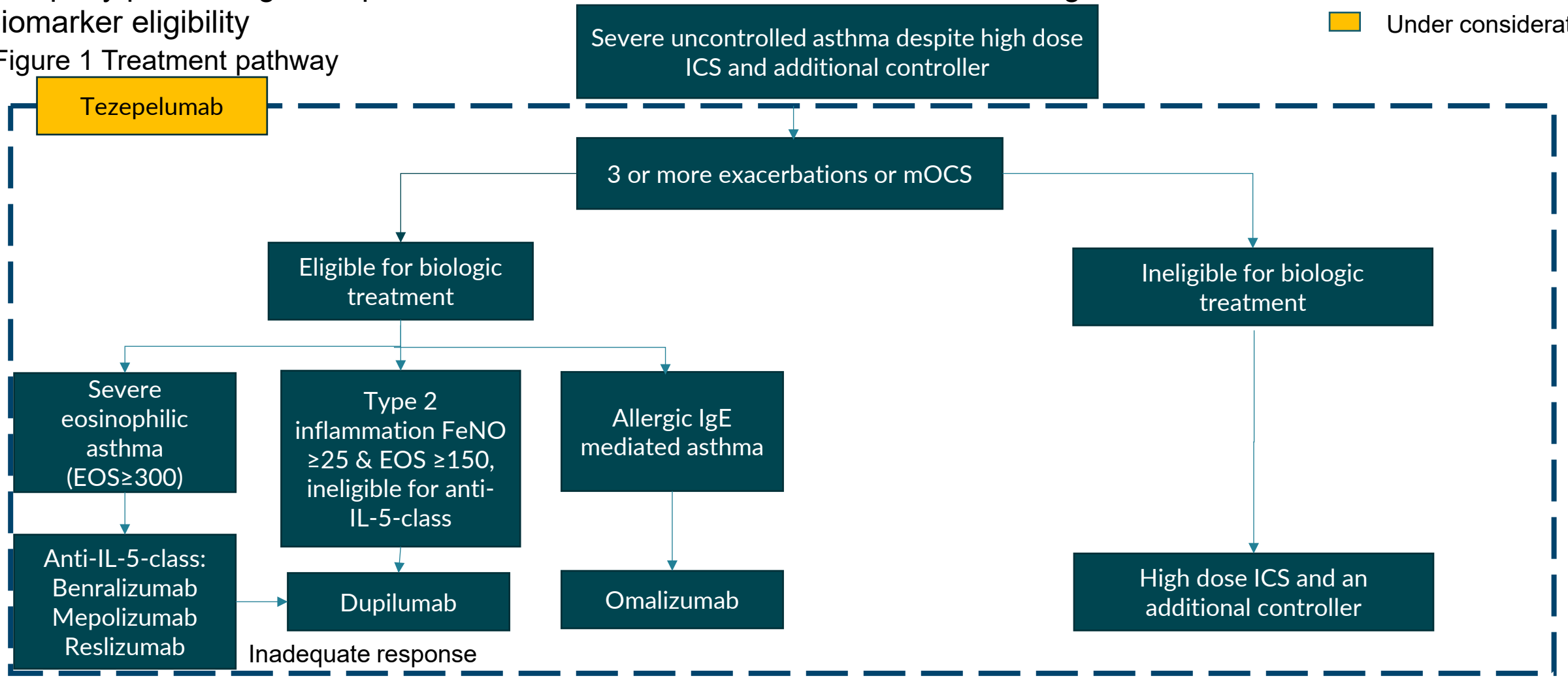
RECAP

Company positioning: tezepelumab as an add-on to first-line standard care regardless of biomarker eligibility

NICE recommended

Under consideration

Figure 1 Treatment pathway



ACD: company's positioning of tezepelumab in treatment pathway appropriate: Relevant comparators for tezepelumab are standard care plus add-on biological treatments, and standard care alone

Abbreviations: ACD, appraisal consultation document EOS, eosinophil; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL: interleukin; mOCS, maintenance oral corticosteroid treatment

Tezepelumab (TEZSPIRE, AstraZeneca)

Company, tezepelumab, first-in-class biologic acting at top of asthma inflammatory cascade

Table 1 Technology details

Marketing authorisation	• Indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment
Mechanism of action	• Anti-TSLP, human monoclonal antibody that binds to human TSLP with high affinity and prevents its interaction with the heterodimeric TSLP receptor
Administration	• [redacted] • [redacted]
Price	• List price, £1,265 per vial • Patient access scheme discount in place (confidential)

Abbreviations: TSL, Thymic stromal lymphopoietin

Company's post-hoc subgroups & NICE's previous appraisals recommended for subpopulations defined by biomarkers

Table 2 Subgroups in recent NICE appraisals and company's additional post-hoc subgroups

Previous technology appraisal	NICE recommendation and subpopulation covered: *Severe refractory eosinophilic asthma in adults only if:*	Additional post-hoc subgroup included by company
Mepolizumab,2021; NICE TA671	• EOS ≥ 300 cells/μl with ≥ 4 exacerbations needing systemic corticosteroids in previous 12 months or had continuous oral corticosteroids or • EOS ≥ 400 cells/μl with ≥ 3 exacerbations needing systemic corticosteroids in previous 12 months	**Anti-IL-5 eligible:** • ≥ 18 years; • EOS ≥ 300 cells/μl (with ≥ 4 exacerbations or mOCS) or, • EOS ≥ 400 cells/μl and 3 exacerbations
Benralizumab, 2019; NICE TA565	• EOS ≥ 300 cells/μl with ≥ 4 exacerbations needing systemic corticosteroids in previous 12 months or had continuous oral corticosteroids or • EOS ≥ 400 cells/μl with ≥ 3 exacerbations needing systemic corticosteroids in previous 12 months	
Reslizumab, 2017; NICE TA479	• EOS ≥ 400 cells/μl and ≥ 3 exacerbations needing systemic corticosteroids in previous 12 months	

Abbreviations: EOS, blood eosinophil count; FeNO: fractional nitric oxide; IgE, immunoglobulin E; OCS, oral corticosteroids; mOCS, maintenance oral corticosteroid; ppb, parts per billion

Company's post-hoc subgroups & NICE's previous appraisals recommended for subpopulations defined by biomarkers

RECAP

Table 2 (cont.)- Subgroups in recent NICE appraisals and company's additional post-hoc subgroups

No NICE guidance

Previous technology appraisal	NICE recommendation and subpopulation covered:	Additional post-hoc subgroup included by company
Dupilumab, 2021; NICE TA751	*Severe asthma with type 2 inflammation in people 12 years* and over only if: • EOS ≥ 150 cells/µl, FeNO ≥25 ppb; and ≥4 or more exacerbations in previous 12 months	**Dupilumab eligible:** • ≥ 18 years, EOS 150–299 cells/µl, FeNO ≥ 25 ppb, ≥ 4 exacerbations, and non-mOCS or • adolescent (12–17 years), EOS ≥ 150 cells/µl, FeNO ≥ 25 ppb, ≥ 4 exacerbations, and non-mOCS
Omalizumab, 2013; NICE TA278	*Severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and older* who: • need continuous or frequent OCS (defined as 4 or more courses in the previous year)	**Omalizumab eligible:** • ≥12 year*, IgE ≥ 30, and ≥ 4 exacerbations or mOCS
Non-bio eligible population (no NICE recommendation)	≥ 3 exacerbations or mOCS population who are not currently eligible for biologicals treatment	

* Aligns with marketing authorisation population

NICE

Abbreviations: EOS, blood eosinophil count; FeNO: fractional nitric oxide; IgE, immunoglobulin E; OCS: oral corticosteroids; mOCS, maintenance oral corticosteroid; ppb: parts per billion

Company's model overview

RECAP

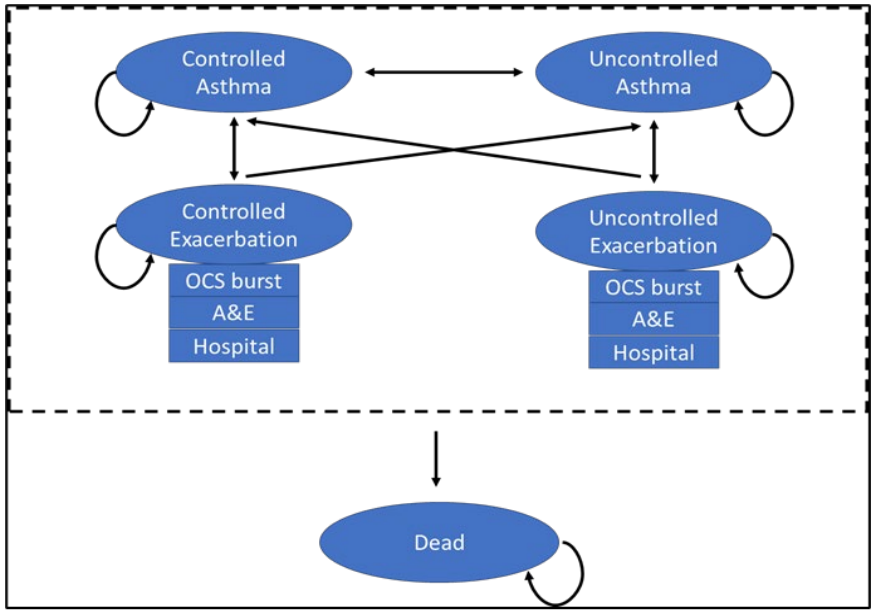
Model uses different set of probabilities post 52 weeks

Table 3 Model structure

Structure		Markov model
Population		People with severe uncontrolled asthma, use of high dose ICS, additional controller, 3+ exacerbations or mOCS (stratified into subgroups)
Health states		**5 health states**: • controlled asthma: ACQ<1.5 • uncontrolled asthma: ACQ ≥1.5 • exacerbation, previously controlled asthma • exacerbation, previously uncontrolled asthma • death: asthma-related mortality & all-cause mortality
Transition probabilities	TEZ	• Pre-assessment response with & without mOCS • Post-assessment response with & without mOCS
	SoC	• Pre-assessment response with& without mOCS, remains constant in model
Time horizon		Lifetime (60 years)
Cycle length		4 weeks
Discounting		3.5% for costs and health effects
Cost and resource use		PSSRU, NHS reference costs, Wilson 2014

Abbreviations: ACQ, asthma control questionnaire; ICS, inhaled corticosteroids; mOCS, maintenance oral corticosteroid treatment; PSSRU, Personal Social Services Research Unit, SoC, standard of care; TEZ, tezepelumab

Figure 2 Model structure



ACD: company's economic model structure is appropriate for decision making

ACD conclusions and uncertainties (1/2)

Table 4 ACD conclusion and uncertainties

	Committee conclusion	To discuss?	ACD
Positioning	• Company's positioning of tezepelumab appropriate	No	3.4
Comparators	• Standard care plus add-on biological treatments, and standard care alone relevant comparators	No	3.5
Treatment response	• 50% reduction would be considered a clinically meaningful reduction • Company's definition of response (any reduction in exacerbations or mOCS dose) from baseline was not appropriate	Yes	3.6
Clinical evidence	• Population generalisable to NHS practice • Tezepelumab is clinically effective in severe asthma compared with placebo • Tezepelumab more effective than placebo in reducing AAER or mOCS in pre-planned and post-hoc subgroups	No	3.7-3.9
Network meta-analyses	• Company's NMAs were highly uncertain • Tezepelumab's clinical effectiveness compared with other biological treatments is unknown	Yes	3.10

Abbreviations: AAER, annualised asthma exacerbation rate; ACD, appraisal consultation document; mOCS, maintenance oral corticosteroids; NMA, network meta-analyses

ACD conclusions and uncertainties (2/2)

Table 4 (cont.)- ACD conclusion and uncertainties

	Committee conclusion	To discuss?	ACD
Model structure	• Appropriate for decision making	No	3.11
ACQ-6 score	• Using ACQ-6 score of 1.5 as cut-off to define asthma control states appropriate	No	3.12
Modelling asthma exacerbations	• Company's approach of modelling exacerbations was acceptable	No	3.13
Transition probabilities	• Company's approach was acceptable	No	3.14
Mortality estimate	• Company's asthma- related mortality estimates, which were closer to the EAG's scenario	Yes/partially	3.15
Utility gain	• Assuming additional utility gain for biological treatments not appropriate	Yes/partially	3.16
Cost-effectiveness estimates	• Not cost effective- reliable ICER could not be determined because of uncertainties	Yes	3.17-3.18

Abbreviations: ACD, appraisal consultation document; ACQ, Asthma Control Questionnaire; ICER; Incremental cost-effectiveness ratio

Consultation responses

NICE National Institute for Health and Care Excellence

ACD consultation responses

Received from

- **Company: AstraZeneca UK**
- **Comparator company: SANOFI**
- **3 patient organisations**:
    - British Society for Allergy & Clinical Immunology (BSACI)
    - British Thoracic Society
    - Asthma + Lung UK
- **NHS England Specialised Commissioning**
- **1 clinical expert**

Abbreviations: ACD, appraisal consultation document.

Clinical expert, patient organisations and comparator company

Unmet need and burden of disease

- “Biologic drugs have given me my life back. I noticed a huge improvement almost immediately and haven’t needed to take steroids since. I can now exercise and have regained my independence and social life...”
- Large unmet need among biologics ineligible population for treatments which can reduce exacerbations and steroids side effects

Comments on ACD conclusion

- IN SOURCE, tezepelumab did not meet primary endpoint of reduction in final daily oral corticosteroid dose at week 48 versus placebo; more data need for people with severe asthma who are dependent on mOCS
- No accepted protocol to define variability of EOS and FeNO within a given individuals with asthma
- Appropriate to use ACQ-6 score of 1.5 as a cut-off to define asthma control status
- Asthma Mortality estimates likely underestimated, would not be collected through Health Survey and Registry data
- Disagreed with committee’s conclusion on utility gain: statistically significant difference in EQ-5D-5L should not be ignored

Comments on recommendation

- “I am quite concerned that 65% of uncontrolled severe asthmatics, particularly those who do not qualify for other biologics will not have the opportunity to try, and potentially benefit from, using tezepelumab”

Abbreviations: ACD, appraisal consultation document; ACQ, Asthma Control Questionnaire; EOS:blood eosinophil counts; EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels mOCS, maintenance oral corticosteroids;

Key issue: Definition of treatment response

ACD conclusion:

- 50% reduction would be considered a clinically meaningful reduction and company's definition of treatment response i.e. any reduction in exacerbations or mOCS dose from baseline not appropriate
- Committee requested further analyses: 50% reduction in exacerbations **and** oral corticosteroids dose applied in model

Company: Updated its base case with treatment response defined as:

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

- Explored following scenario (committee requested) but consider not appropriate for decision making:
  - people not on mOCS: ≥50% reduction in exacerbations
  - people on mOCS: ≥50% reduction in mOCS dose **and** ≥50% reduction in exacerbation
- Consider committee preferred definition inconsistent with clinical practice and previous TA guidance
- Sets a high bar for tezepelumab response, most people would not achieve this and would discontinue tezepelumab
- Clinical expert opinion to company: for people on mOCS a ≥50% reduction in mOCS dose is an appropriate definition of treatment response regardless of exacerbation reduction

Abbreviations: ACD, appraisal consultation document; mOCS, maintenance oral corticosteroids: TA, technology appraisal

Key issue: Definition of treatment response

British Thoracic Society (BTS):

- Company's definition of treatment response was not appropriate
- Treatment response should be defined as 50% reduction in exacerbation **OR** 50% reduction in mOCS dose within the first 12 months

EAG:

- Noted differences in transition probabilities in updated base case: showing favourable probabilities for the tezepelumab compared with original base case
- Discontinuation rates for people having tezepelumab in most subgroups (except non-biological eligible) in mOCS population lower than original base: lacks face validity
- Preferred to align with committee's preferred definitions of treatment response: 50% reduction in exacerbation frequency **and** 50% reduction in mOCS dose within first 12 months

What is the appropriate definition of treatment response?

Abbreviations: ACD, appraisal consultation document; mOCS, maintenance oral corticosteroids: TA, technology appraisal

Key issue: Uncertainty in the NMA (1/2)

ACD conclusion:

- Biomarker evidence informing NMA did not match biomarkers used for NICE-recommended treatments
- Company's NMA highly uncertain, tezepelumab's clinical effectiveness compared with biologicals is unknown

Company:

- Consider alternative approach suggested would increase uncertainty in results. Previous biologics only recommended in subpopulation: not clinically & cost-effective in full licensed populations
- ITT- based NMA associated with greater uncertainty:
  - would assume all populations in NMA are comparable and
  - would not reflect clinical practice (NICE recommended population)
- Explored uncertainty associated with NMA by conducting sensitivity analyses based on simulated treatment comparison (STC) and NMA data from recent publication (Ando et al 2022)
- Company updated its base case NMAs informing comparisons to improve consistency:
  - For reslizumab subgroup: EOS ≥300 cells/µl informed comparison with reslizumab, mepolizumab and benralizumab
  - Data from Hospitalised AAER NMA informed by ITT population in original base is not used in revised model
  - Updated NMAs for dupilumab using data on 200 mg instead of 300 mg dose
- Provided scenario analyses using alternative subgroup data for benralizumab, reslizumab and dupilumab (AAER NMA) and based on STC data to inform AAER and OCS sparing (using ITT population)

Abbreviations: AAER, annualised asthma exacerbation rate; ACD, appraisal consultation document; EOS, blood eosinophil count; ITT, intention to treat; NMA, Network meta-analyses

Key issue: Uncertainty in the NMA (2/2)

EAG:

- NMA conduct appropriate but unresolvable uncertainty in NMA linked to the challenges in matching to the appropriate biological subgroups for comparators
- Uncertainties in NMA not resolved by provided analyses or assertions provided by company:
  - STC not suitable verifying NMA results - comparison have different distribution of effect modifier and STC is a series of pairwise comparison instead of a joined up network
  - Company's comparison with published NMA useful but does not address uncertainty
  - Uncertainty due to follow-up times not amenable of categorisation: mOCS reduction in placebo arm would benefit from more attempts at reduction, same would apply for tezepelumab
- Agreed with company's updated base for AAER and OCS reduction from the high EOS (≥300 cells/µl) subgroup for anti-IL5 and reslizumab subgroups
- No data provided on impact of using data on 200 mg dose instead of 300 mg for dupilumab NMA
- EOS ≥150 cells/µl most appropriate thus retained for base case for dupilumab subgroup NMA
- EAG retained original NMA to inform its base case

Has the response submitted by the company sufficiently resolved the uncertainties in NMA?

NICE

Abbreviations: AAER, annualised asthma exacerbation rate; ACD, appraisal consultation document; EOS, blood eosinophil count; OCS: oral corticosteroids; ITT, intention to treat; STC, simulated treatment comparison

Additional issues not requested by the committee

Additional issues: Utility gain with biologic therapy

ACD conclusion: assuming additional utility gain for biological therapy not appropriate

Company:

- Had an error in its original base case: co-efficient for biologic-specific utility no longer statistically significant
- Removed utility gain in its updated base case

EAG:

- Noted re-estimation of health state utility regression yields point estimates for disutility associated:
  - with an A&E attendance of [redacted]
  - and [redacted] for mOCS burst
- Point estimates lack face validity; expect disutility associated with A&E more severe than mOCS burst
- Consider point estimates are highly susceptible to sampling error
- Retained these estimates but provided scenarios however this did not have an impact on the overall results:
  - assuming an equal disutility between two
  - reversal of point estimates

Is the committee satisfied with the company's updated utility values?

Abbreviations: ACD, appraisal consultation document; A&E, accident and emergency; mOCS, maintenance oral corticosteroids

Additional issue: All-cause mortality (1/2)

ACD conclusion:

- Company's mortality estimates were appropriate for decision making
- Company's estimates were based on HSE asthma report 2018 and EAG estimates from TA565

Company: ACD: noted "there may be additional benefits of tezepelumab not captured but this is uncertain"

- Conducted a real world study (UK-CPRD-ONS) based on CPRD data of all cause mortality in non-biologic eligible subgroup to inform its updated base case and also provided scenario analyses
- UK-CPRD ONS was based on non-biologic population from 2012-2017: company considers this group reflective of clinical practice when biologics usage was low in clinical practice
- Results align with Roche et al (French study): all-cause mortality for severe uncontrolled higher than its model
- Chosen non-biologic eligible to calibrate mortality in standard care (without biologic) arm to UK-CPRD results
- Applied multiplier to original exacerbation-related mortality probabilities to standard care (non-biologic) to yield 10-year all-cause mortality for each age band as UK CPRD-ONS study

EAG: UK-CPRD study well conducted and appropriate source but concerned how results implemented in model:

- Noted sample sizes reported for overall population (n=[redacted]) and for each subgroup but results were based on biologic eligible population (n= [redacted]) which were applied for all subgroups in model: not appropriate approach
- More appropriate to apply full target population across all subgroups for precise estimates or using mortality rates by subgroup be applied to their respective mortality rates individually in model

Abbreviations: ACD, appraisal consultation document; CPRD, Clinical Practice Research Datalink; HSE: Health Survey England;ONS, Office for National Statistics

Additional issue: All-cause mortality (2/2)

EAG:

- Data extraction time period from CPRD excluded biologic therapy to minimise contamination with biologicals
- Multipliers uncertain due to sampling uncertainty: due to limited sample size of CPRD study and rarity of mortality events
- Considers company's model underestimates uncertainty in mortality estimates
- While calibrating exacerbation-related mortality to all-cause mortality overestimate modelled mortality
- Flagged a paper by Engelkes et al. 2020 (multinational cohort study): compared UK CPRD data from 2008-2013 reported lower all-cause mortality rates than company's CPRD analysis: cause death not reported 80% cases in CPRD

Table 5 All-cause mortality rates* (original and revised base case)

Age group (years)	Mortality (SoC-original model)	Mortality (CPRD-revised model)
50<60	[redacted]	[redacted]
60<70	[redacted]	[redacted]
70<80	[redacted]	[redacted]
80<90	[redacted]	[redacted]
90+	[redacted]	[redacted]

* Expressed as number of deaths per 1000 PY

Table 6 All-cause mortality rates* (Engelkes et al)

Age group (years)	Mortality (Engelkes et al)
45<55	4.0
55<65	6.7
65<75	14.6
>=75	54.6

NICE

Are the company's updated all-cause mortality rates acceptable for decision making?

Abbreviations: ACD, appraisal consultation document; CPRD, Clinical Practice Research Datalink; ONS, Office for National Statistics, SoC, standard of care; PY, patient years

Company & ERG base case assumptions

Table 7 Company and ERG base case

Assumption	Company base case	ERG base case
Treatment response definition	• People not on mOCS: ≥50% reduction in exacerbations • People on mOCS: ≥50% reduction in mOCS dose • Scenario (committee requested)	• People not on mOCS: ≥50% reduction in exacerbations • People on mOCS: ≥50% reduction in mOCS dose **and** 50% reduction in exacerbations

Uncertainties in NMA resolved?	• No
	  • Updated data for anti-IL-5 eligible population
	  • NMA data relating to the 200mg dose of dupilumab was used
		• Not completely
		• ACM1 base case no changes

Additional utility gain applied?	• Committee preferred (ACM1)	• Committee preferred (ACM1)
Mortality	• Based on UK CPRD-ONS data	• Committee preferred (ACM1)

NICE

Abbreviations: ACM1, first appraisal committee meeting; CPRD, Clinical Practice Research Datalink; mOCS, maintenance oral corticosteroids; ONS, Office for National Statistics; TA: technology appraisal

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Summary

- Company's updated base case results in ICERs that are **lower** than what would **usually** be considered a cost-effective use of NHS for all subgroups
- ERG's base case results in ICERs that are **higher** than what would **usually** be considered cost-effective use of NHS resources in some subgroups

Abbreviations: ICER, Incremental cost-effectiveness ratio

NICE National Institute for Health and Care Excellence

Thank you.

Back up slides

NICE National Institute for Health and Care Excellence

Key clinical trials: PATHWAY, NAVIGATOR & SOURCE

RECAP

Table 8 Clinical trial designs and outcomes

	PATHWAY	NAVIGATOR	SOURCE
Design	Phase II, double-blinded	Phase III, double-blinded	Phase III, double blinded
Population (n)	Adult with inadequately controlled, severe asthma (n=550)	Adult and adolescent with severe, uncontrolled asthma (n=1,059)	Adult with severe, mOCS-dependent asthma (n=150)
Intervention	Tezepelumab 210 SC Q4W + SoC (n=137)*	Tezepelumab 210 mg SC Q4W + SoC (n=528)	Tezepelumab 210 mg SC Q4W plus ICS/LABA and mOCS + SoC (n=74)
Comparator (n)	Placebo (n=138)	Placebo (n=531)	Placebo (N=76)
Treatment duration	52 weeks, follow-up 12 weeks	52 weeks, follow-up 12 weeks	48 weeks, follow-up 12 weeks
Primary outcome	AAER measured at Week 52	AAER measured at Week 52	% reduction in OCS at Week 48
Locations	98 centres (12 countries)	297 centres (18 countries)	60 centres (7 countries)
Inclusion criteria	ACQ-6 score ≥1.5; ≥2 asthma exacerbations or ≥1 severe asthma exacerbations resulting in hospitalisation within 12 months	ACQ-6 score ≥1.5 at screening; ≥2 asthma exacerbations within 12 months	≥1 asthma exacerbation event within 12 months
Used in model?	Yes	Yes	Yes

* Relevant dose for this appraisal

NICE

Abbreviations: ACQ: asthma control questionnaire; AAER: annualised asthma exacerbation rate; ICS: inhaled corticosteroid; LABA; long-acting beta agonist; mOCS: maintenance oral corticosteroid treatment; Q4W; once every 4 weeks; SC: subcutaneous; SoC: standard of care;

Clinical trial results: Annualised Asthma Exacerbation Rate (AAER)

Tezepelumab reduced AAER in **PATHWAY** and **NAVIGATOR**; but reduction [redacted] in **SOURCE**

Table 8 PATHWAY, NAVIGATOR and SOURCE

Outcome	PATHWAY[a] 52 weeks		NAVIGATOR[b] 52 weeks		SOURCE[b] 48 weeks	
	Tezepelumab n=137	Placebo n=138	Tezepelumab n= 528	Placebo n=531	Tezepelumab n=[redacted]	Placebo n=[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]	

*Rate = total number of asthma exacerbations in each group/total person-year follow-up in each group; 95% CI for rate based on the exact 95% Poisson CI. Rate ratio and 95% CI for rate ratio estimated from negative binomial regression with treatment group, and the stratification factors - baseline blood eosinophil count (≥ or < 250 cells/μL) and baseline ICS dose level (medium or high) as covariates.

[a] ITT population; [b]: FAS population

Abbreviations: CI: confidence interval; ICS: inhaled corticosteroid;

Source: Table 11 and 14, EAG report

Clinical trial results: AAER related hospitalisation/ED visits

Tezepelumab reduced AAER related ED visits or hospitalisation in **PATHWAY & NAVIGATOR** at 52 weeks, but not in **SOURCE**; no subgroup analysis for this outcome

Table 9 PATHWAY, NAVIGATOR and SOURCE (AAER related to hospitalisation/ED visits)

Outcome	PATHWAY 52 weeks		NAVIGATOR 52 weeks		SOURCE 48 weeks	
	Tezepelumab	Placebo	Tezepelumab	Placebo	Tezepelumab	Placebo
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAER (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]		[redacted]		[redacted]	
P-value	[redacted]		[redacted]		[redacted]	

NICE

Abbreviations: AAER, annualised asthma exacerbation rate; CI, confidence interval; ED: emergency department

Clinical trial results: change from baseline in OCS*

Greater % reduction in OCS in tezepelumab compared with placebo from baseline at 48 week in **SOURCE**, but difference not [redacted]

Table 10 Percentage reduction from baseline in final daily OCS dose at Week 48 (FAS)

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

* Primary outcome of SOURCE. PATHWAY and NAVIGATOR did not assess this outcome

Abbreviations: CI: confidence interval; FAS: full analysis set; OCS: oral corticosteroids; OR: odds ratio

Clinical trial results: change in EQ-5D-5L^ score from baseline

Greater improvement in EQ-5D-5L score in tezepelumab compared with placebo in **NAVIGATOR** and **SOURCE**

Table 11 EQ-5D-5L score change from baseline at Week 52 (NAVIGATOR) and Week 48 (SOURCE)

Outcome	NAVIGATOR 52 weeks		SOURCE 48 weeks	
	Tezepelumab n=528	Placebo n=531	Tezepelumab [redacted]	Placebo [redacted]
n	[redacted]	[redacted]	62	58
LS mean CFB to week 52	[redacted]	[redacted]	9.21 (2.209)	2.00 (2.226)
LS mean difference (95% CI)	[redacted]		7.21* (1.01, 13.41)	
P-value	[redacted]		0.023	

^ EQ-5D-5L not assessed in PATHWAY; * Measurement in EQ-5D-5L visual analogue scale scores;

NICE

Abbreviations: Asthma Control Questionnaire (ACQ-6); CI, confidence interval; EQ-5D-5L; European Quality of Life-5 Dimensions-5 Levels; LS: least squares; NR: not reported

Subgroup analysis results for AAER and OCS

Tezepelumab generally more effective than placebo in pre-planned and post-hoc subgroups across trials

Pre-planned subgroups:

- In PATHWAY and NAVIGATOR, tezepelumab largely more effective in reducing AAER in subgroups stratified by blood EOS, FeNO, prior exacerbations, and inhaled corticosteroids categories (ICS) at 52 weeks

- In SOURCE, tezepelumab more effective in reducing OCS in subgroups with higher baseline [redacted] at 48 weeks

Post-hoc subgroups:

- In NAVIGATOR, tezepelumab reduced AAER in most post-hoc subgroups, but not for dupilumab eligible subgroup at 52 weeks

- In SOURCE, tezepelumab only reduced AAER in anti-IL-5 eligible subgroup at 48 weeks

Abbreviations: AAER: annualised asthma exacerbation rate; EOS: eosinophil; FeNO: fractional exhaled nitric oxide; OCS: oral corticosteroids

NMA results for: AAER, AAER-related hospitalisation (ITT), and OCS reduction

Tezepelumab only better than placebo in reducing AAER and OCS in most subgroups stratified by biomarkers; and in reducing AAER related hospitalisations in ITT population

Statistically significant advantage

Numerical advantage

Table 12: NMA results for outcomes informed the model

[redacted]

Abbreviations: AAER: annualised asthma exacerbation rate; BEN: benralizumab; CrL: credible interval; DUP: dupilumab; EOS: blood eosinophil count; FeNO: fractional nitric oxide; ITT: intention-to-treat; NA: not applicable; OCS oral corticosteroids; OM; omalizumab; PBO: placebo: ppb: parts per billion RES: reslizumab; MEP: mepolizumab

Is tezepelumab clinically effective compared with other biological therapies?

Summary of company changes (2/2)

Table 13 ACM1 and ACM2 assumptions in company base case

Issue		Company base case (ACM1)	Company base case (ACM2)
Asthma mortality	Exacerbation-related mortality age bands logic	Age band-specific exacerbation-related mortality rates applied up to one year too early in the model	Age band-specific mortality only applied once patient reaches the age corresponding to the lower limit of the age band in question
	Exacerbation-related mortality probabilities	Exacerbation-specific mortality inputs from Watson 2007, Roberts 2013 and National Review of Asthma Deaths report	Align with age-specific real world UK mortality data collected in the non-biologic eligible population of interest
Utilities gain on biologic		Utility gain on biologics	No utility gain on biologics
Unit costs		Unit costs reflect 2020/21	Unit costs reflect 2022/23
Discontinuation probability at response assessment in mOCS treated population		Assumed to equal that of non-mOCS treated population	Calculated from SOURCE population

Abbreviations: ACM1, first appraisal committee meeting, ACM2: second appraisal committee meeting; mOCS, maintenance oral corticosteroids:

Summary of company changes (1/2)

Table 13 (cont.) ACM1 and ACM2 assumptions in company base case

Issue		Company base case (ACM1)	Company base case ACM2
Exclusion of reslizumab		Excluded people on mOCS	Included people on mOCS
NMA for reslizumab eligible	AAER	Benralizumab - NMA 3+ exacerbations	Benralizumab - NMA EOS High: ≥300 cells/µl
		Mepolizumab - NMA ITT	Mepolizumab - NMA EOS High: ≥300 cells/µl
		Reslizumab - NMA 3+ exacerbations	Reslizumab - NMA E0S High: ≥300 cells/µl
	OCS	Benralizumab - NMA ITT	Benralizumab - NMA EOS High: ≥300 cells/µl
		Mepolizumab - NMA ITT	Mepolizumab - NMA EOS High: ≥300 cells/µl
		Reslizumab - Assumption, equal to tezepelumab (due to lack of data)	Reslizumab - Assumption, equal to tezepelumab (due to lack of data)
NMA	Dupilumab eligible	Data for 300 mg dose was used	Data related 200 mg dose used NMA (NICE recommended)
Treatment response		Any reduction in exacerbations or mOCS dose	• People not on mOCS: ≥50% reduction in exacerbations • People on mOCS: ≥50% reduction in mOCS dose

Abbreviations: AAER, annualised asthma exacerbation rate; ACM1, first appraisal committee meeting, ACM2: second appraisal committee meeting; EOS, blood eosinophil count; ITT, intention to treat; NMA, network meta-analyses; mOCS, maintenance oral corticosteroids: