Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

Part 1 slides for public

Technology appraisal committee B, 7 May 2025

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Company: AstraZeneca

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) (1/2)

Rare autoimmune disease with a serious impact on patients' lives

Cause

- High levels of eosinophils (a type of white blood cell) in circulation and tissues
- Leads to inflammation in blood vessels (vasculitis), restricting blood flow to tissues and organs

Epidemiology

- Around 2,600 people in England have EGPA
- Median age of diagnosis 57; very rare in children

Diagnosis

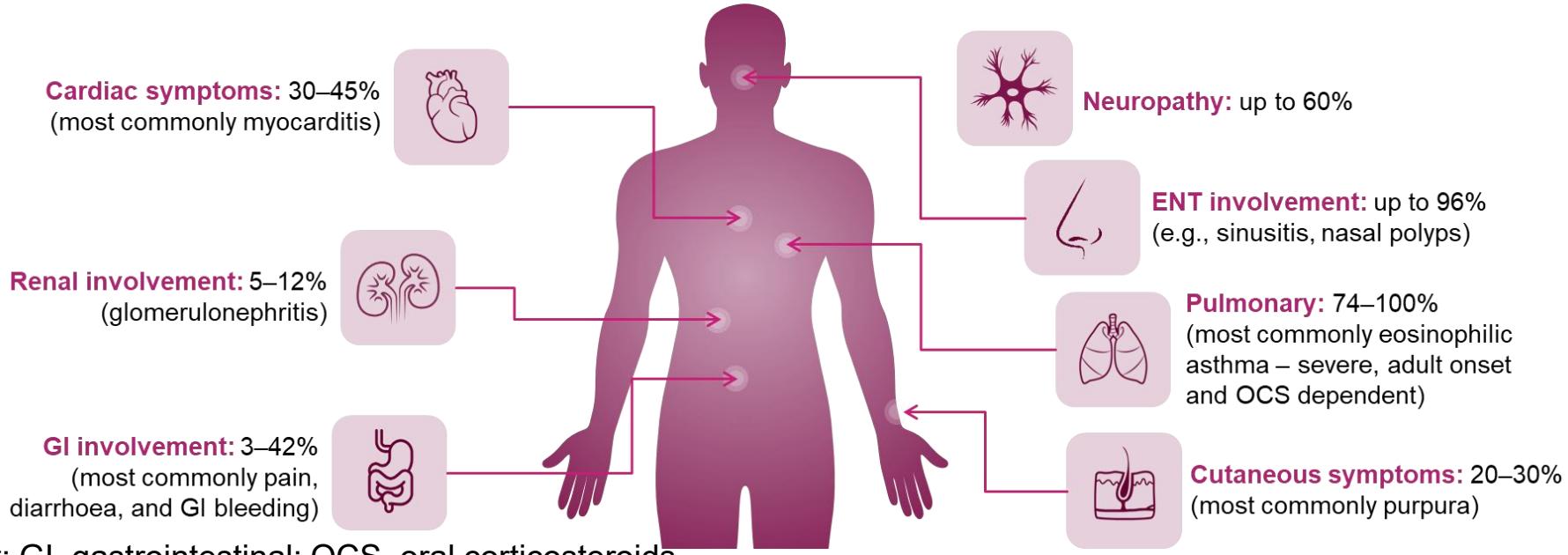
- Difficult – takes around 7 to 12 years; tests involve blood, lungs, tissue and heart
- Delay in diagnosis can mean worse disease, progression and disease burden as patients present with a broader range of manifestations and associated symptoms contributing to organ damage, requiring additional steroid and immunosuppressive treatment to try to induce remission
- Complex diagnoses lead to repeated hospital visits and worsening symptoms over time
- Can leave patients feeling anxious, depressed, confused and frustrated as they struggle with the uncertainty of their health

OCS, oral corticosteroids

Background on relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) (2/2)

Symptoms and prognosis

- Asthma is one of main symptoms and may begin many years before other symptoms; people with severe eosinophilic asthma can have benralizumab as recommended in TA565
- Later symptoms may include rashes, joint pain and swelling, peripheral neuropathy, abdominal pain, diarrhoea, shortness of breath, arrhythmia, presence of red blood cells in urine, chest pain, and heart failure
- Relapse means worse symptoms and more organ damage; at least 50% relapse after treatment in 5 years
- Refractory defined as no remission in 6 months, worse symptoms, need for high doses of OCS
- For more detail see EGPA health states



ENT, ear nose and throat; GI, gastrointestinal; OCS, oral corticosteroids

Patient perspectives

Submission from Vasculitis UK and 1 patient expert

- Chronic condition, flare ups and relapse common
- Rare, serious disease: early, targeted intervention needed before substantial damage is done to get people into remission quickly
- Nerve and joint pain plus respiratory issues from asthma reduce mobility; isolation because people shield to avoid getting infections
- Most common treatments corticosteroids, cyclophosphamide and mycophenolate; mepolizumab and benralizumab available in some regions through asthma clinics
- Side effects from steroids common; treatment with immunosuppressants does not always mean a reduction in steroids
- Benralizumab controls EGPA and asthma, fewer chest infections, reduced steroids, better quality of life, fewer hospital appointments

My symptoms included lung pain, coughing, fatigue, weakness, joint pain, numbness, pins and needles, night sweats, trouble sleeping, headaches, breathlessness, sinus issues, rashes; my mobility was severely affected, which affected my work routine

Benralizumab has been life changing for me. I am able to lead a normal life. Work and home life is better. My asthma is under control

Side effects [of high dose steroids (prednisolone)] were bad: woolliness, memory issues, mania, bad temper, difficulty sleeping, weight gain
Mycophenolate and azathriopine: 24/7 pain
No adverse effects with benralizumab to date (2 years +) and off prednisolone

Clinical perspectives

First EGPA-specific treatment; likely to increase length and quality of life

Submissions from the Association of Respiratory Nurses, British Society for Rheumatology, UK and Ireland Vasculitis Rare Disease Group, UK Kidney Association, and 1 clinical expert

- Aim of treatment: disease control, prevent organ damage, OCS reduction, improve quality of life
- Clinically significant response: disease remission, corticosteroid reduction, reduced emergency care
- Unmet need for targeted approach, care pathway not well defined
- Few side effects with benralizumab in clinical practice; significant harm from long-term effects of current treatments
- Benralizumab first medicine specifically for EGPA; step-change in care
- Would reduce hospital visits, outpatient clinic use and OCS side effects in the long term; benefits to patients and NHS health economy
- Would standardise pathways and equity of access to IL5 inhibition for people with EGPA
- Expect benralizumab to increase length and quality of life; administration by subcutaneous injection at home; no specific blood monitoring needed, unlike for conventional DMARDS and cyclophosphamide

DMARD, disease-modifying antirheumatic drug; IL5, interleukin-5; OCS, oral corticosteroid

Equality considerations

Home administration

- Expert groups noted that because benralizumab is administered at home, socioeconomic disparities in education level, healthcare literacy and access to healthcare resources could affect ability to manage treatment; cultural and language barriers could also be an issue
- This is in common with other subcutaneous treatments

Restriction to non-severe EGPA

- The EAG noted that restricting benralizumab to non-severe EGPA could disadvantage older people, who are more likely to have severe disease
- Noted during scoping that cyclophosphamide (current treatment for severe EGPA) can cause infertility; so women of childbearing age potentially face a disproportionate harm from cyclophosphamide

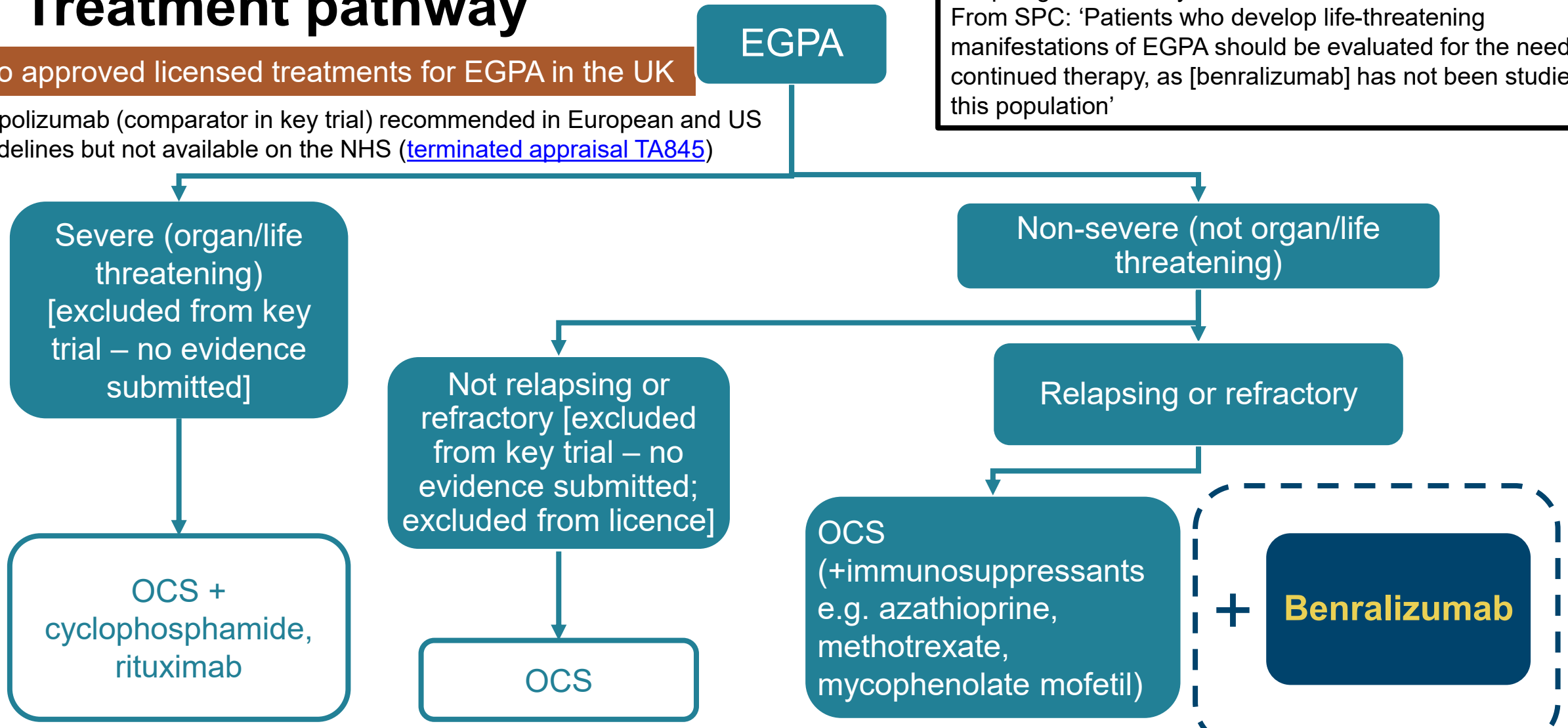
EAG, external assessment group

Treatment pathway

MA wording: as an add-on treatment for adult patients with relapsing or refractory EGPA
From SPC: 'Patients who develop life-threatening manifestations of EGPA should be evaluated for the need for continued therapy, as [benralizumab] has not been studied in this population'

No approved licensed treatments for EGPA in the UK

Mepolizumab (comparator in key trial) recommended in European and US guidelines but not available on the NHS (terminated appraisal TA845)



Is this the right pathway of care for people with EGPA? What are the appropriate comparators for benralizumab?

MA, marketing authorisation; OCS, oral corticosteroid; SPC, summary of product characteristics; TA, technology appraisal

Technology (Fasenra, AstraZeneca)

Marketing authorisation	Benralizumab is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis
Mechanism of action	• Monoclonal antibody • Inhibits eosinophils by binding to IL5 receptor • Causes apoptosis of eosinophils through antibody-dependent cell-mediated cellular cytotoxicity by binding to receptors on immune effector cells (for example, natural killer cells)
Administration	• 30 mg subcutaneous injection every 4 weeks
Price	• £1,955 per 30 mg pre-filled pen • £25,415 for 12 months of treatment • Patient access scheme applies

IL5, interleukin-5

Key issues

No	Issue	ICER impact
1	Generalisability to severe EGPA	Unknown
2	Utility values for refractory and relapse states	Moderate
3	Benralizumab discontinuation rate	Small
4	Relationship between benralizumab and OCS discontinuation	Moderate
5	OCS discontinuation	Small
6	No treatment waning	Large

OCS, oral corticosteroid

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Key clinical trials

BVAS, Birmingham Vasculitis Activity Score; IS, immunosuppressant; OCS, oral corticosteroid

	MANDARA NCT04157348 (n=140)	MIRRA NCT02020889 (n=136)
Design	Phase 3, randomised, double blind, active controlled, non-inferiority	Phase 3, randomised, double-blind, placebo controlled
Population	Adults with refractory or relapsing non-severe (not organ or life threatening) EGPA	Adults with refractory or relapsing non-severe (not organ or life threatening) EGPA
Intervention	**Benralizumab** + OCS (with or without IS)	**Mepolizumab** + OCS (with or without IS)
Comparator	**Mepolizumab** + OCS (with or without IS)	**Placebo** + OCS (with or without IS)
Duration	52 weeks	52 weeks
Primary outcome	% remission (BVAS=0 + OCS dose ≤4 mg/day) at weeks 36 and 48	Accrued remission over 52 weeks and % remission at weeks 36 and 48 (BVAS=0 + OCS dose ≤4 mg/day)
Key secondary outcomes	Accrued remission duration, time to first relapse, OCS use weeks 48 to 52, clinical benefit and complete response, annualised relapse rate, remission maintenance (BVAS=0 + OCS dose ≤7.5 mg/day remission definition for some outcomes)	Accrued remission duration, time to first relapse, OCS use weeks 48 to 52, remission maintenance, % remission at weeks 36 and 48, % remission week 24 until 52 (BVAS=0 + OCS dose ≤7.5 mg/day remission definition for some outcomes)
Locations	International (n=18 UK)	International (n=13 UK)
Used in model?	Yes	Yes (part of indirect treatment comparison)

MANDARA trial results

Benralizumab met the primary endpoint, showing non-inferiority to mepolizumab

Treatment group	Number (%) of patients in remission	Adjusted remission rate (%)	Comparison between groups		
			Difference in remission rates (%)	95% confidence interval	p value
Benralizumab 30 mg (n=70)	40 (58)	57.7	1.2	-14.1 to 16.5	0.88
Mepolizumab 300 mg (n=70)	40 (57)	56.5	-	-	-

Remission defined as a BVAS score of 0 and OCS use of 4 mg/day or less

BVAS, Birmingham Vasculitis Activity Score; OCS, oral corticosteroid

Bucher ITC and MAIC

Compared with standard care alone, benralizumab showed a statistically significant improvement in % in remission at both weeks 36 and 48

- Bucher ITC including MANDARA and MIRRA, with mepolizumab as common comparator, to compare benralizumab with standard care
- EAG satisfied with approach overall; but concern that some people in placebo arm of MIRRA could have joined MANDARA; company said unlikely – MIRRA 5 years before MANDARA; many switched to mepolizumab via LAP so not eligible for MANDARA
- MAIC done to account for uncertainties in ITC; EAG: appropriate, results reflected Bucher ITC

Outcome	Bucher ITC (used in model)	MAIC
% in remission at both weeks 36 and 48 (BVAS=0 and OCS ≤4 mg/day)	OR 17.75 (95% CI 3.33 to 94.67)	OR 20.27 (95% CI 3.26 to 126.16)
Annualised relapse rate	RR 0.57 (95% CI 0.28 to 1.15)	RR 0.49 (95% CI 0.24 to 1.01)

BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; EAG, external assessment group; ITC, indirect treatment comparison; LAP, long-term access programme; MAIC, matching-adjusted indirect comparison; OCS, oral corticosteroids; OR, odds ratio; RR, rate ratio

Unknown effect on ICER

Key issue 1: generalisability to severe EGPA

Background

- People with severe EGPA/who have had cyclophosphamide or rituximab (option for more severe EGPA) excluded from 2 key clinical trials, MANDARA and MIRRA
- Severe EGPA = life threatening manifestations and/or organ impairment linked to long-term poor prognosis

Company

- Understandable clinicians interested in using benralizumab for severe EGPA given limited treatment options but intended positioning not in people currently experiencing severe EGPA
- MANDARA designed to be head-to-head, non-inferiority study to mepolizumab (MIRRA) because mepolizumab was expected to be standard care at this point so MANDARA aligned to MIRRA
- People with a history of severe disease could be included in MANDARA

EAG comments

- Clinical advice that benralizumab could be treatment option for severe EGPA
- CPRD data shows that around a quarter of people have severe EGPA and would be excluded
- No cost effectiveness evidence in this patient group so uncertainty about cost effectiveness modelling
- Clinical advice that relapses could cause organ/life threatening disease manifestations so proportion ineligible could increase over time
- Subgroup analyses in MANDARA and MIRRA suggest greater improvement in remission with benralizumab or mepolizumab respectively in more severe disease (also evidence in severe eosinophilic asthma)

Should people with severe EGPA be included in the recommendation?

CPRD, Clinical Practice Research Datalink

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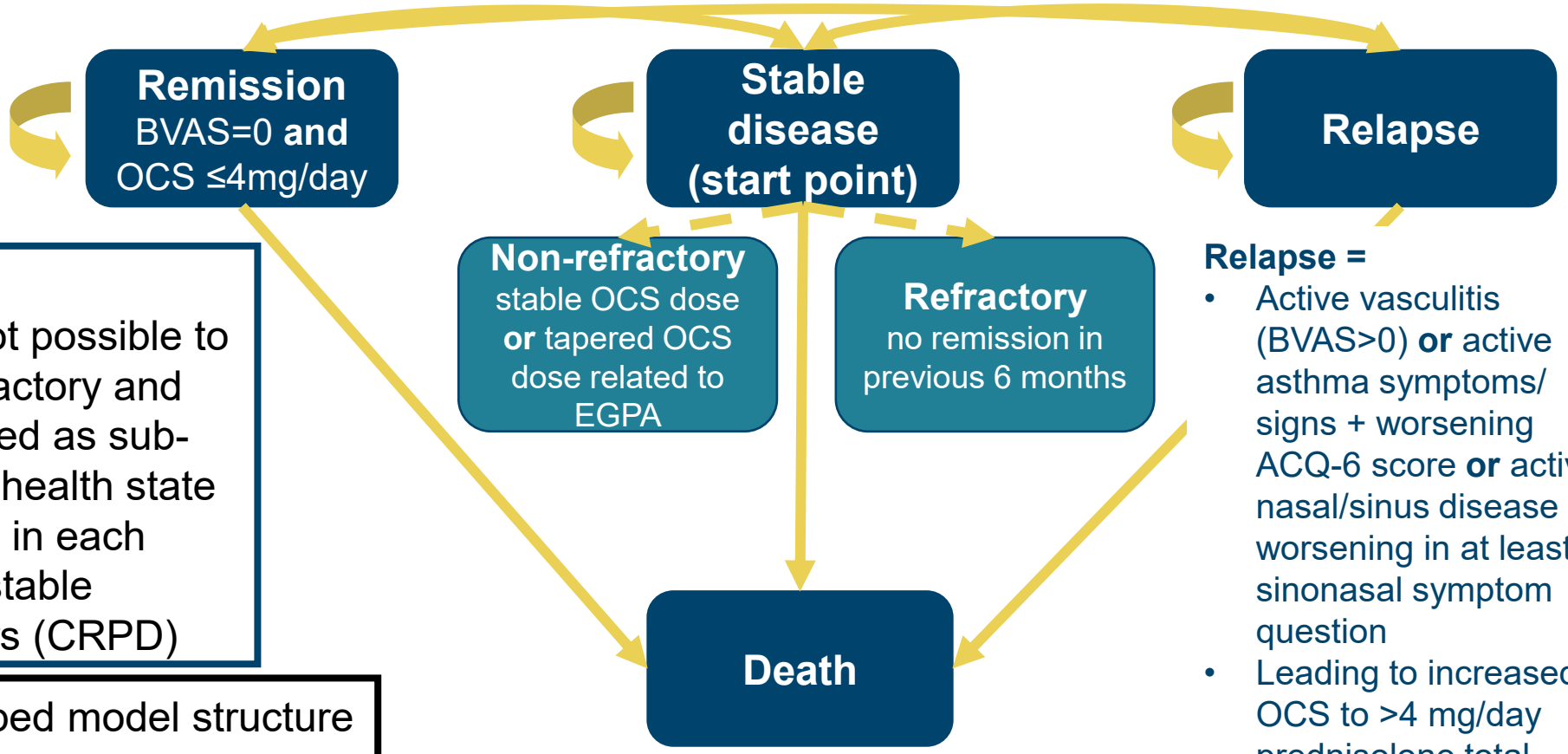
Company's model overview (1/3)

Markov state-transition model with 4-week cycle length

Is the model structure appropriate?



Company:

- Data limitations meant not possible to inform transitions for refractory and non-refractory, so modelled as sub-states of 'stable disease' health state with constant proportions in each
- People start model with stable disease aged [redacted] years (CRPD)

EAG: satisfied with developed model structure

OCS sub-model incorporated in Markov model framework to capture long-term health benefits and cost savings of reduced OCS use associated with benralizumab

Relapse =

- Active vasculitis (BVAS>0) **or** active asthma symptoms/ signs + worsening ACQ-6 score **or** active nasal/sinus disease + worsening in at least 1 sinonasal symptom question
- Leading to increased OCS to >4 mg/day prednisolone total daily dose **or** increased/ addition of IS therapy **or** hospitalisation related to EGPA worsening

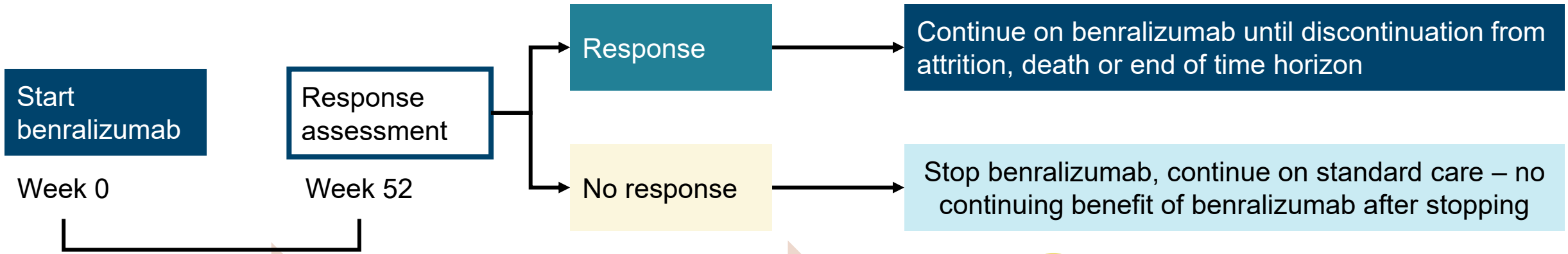
NICE

ACQ-6, Asthma Control Questionnaire; BVAS, Birmingham Vasculitis Activity Score; CPRD Clinical Practice Research Datalink; EAG, external assessment group; IS, immunosuppressant; OCS, oral corticosteroid

Company's model overview (2/3)

Stopping criteria and transition probabilities in benralizumab arm

- Model stopping criteria: response assessment at 52 weeks (consistent with how benralizumab is recommended in severe asthma, and how it's anticipated to be used in EGPA in UK clinical practice)
  - Response defined as BVAS=0 and an OCS dose ≤4 mg/day (primary endpoint of MANDARA)
  - Responders continue on benralizumab
  - Non-responders stop benralizumab and continue on standard care alone
- Everyone who stops benralizumab is subject to standard care transition probabilities
- Probability of response at assessment: [redacted]%; transition probabilities in benralizumab arm from MANDARA



Transition probability derived from everyone in MANDARA

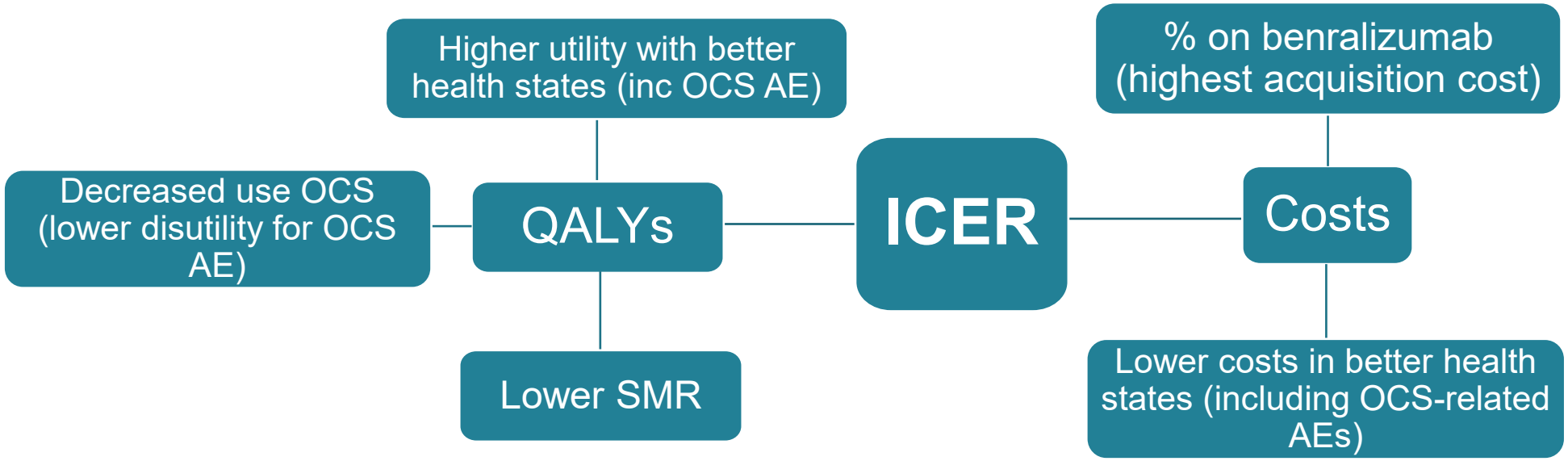
Transition probability derived from subgroup of responders in MANDARA

Are the stopping criteria reasonable in clinical practice?

BVAS, Birmingham Vasculitis Activity Score; OCS, oral corticosteroid

Company's model overview (3/3)

Technology affects costs and QALYs by:



Assumptions with greatest ICER effect:

- no treatment waning (key issue 6)
- people who stop OCS and those who do not are equally likely to stop benralizumab, and if people stop OCS they do not restart OCS if they stop benralizumab (key issue 4)
- effectiveness of standard care the same with or without OCS (key issue 4)
- benralizumab discontinuation rate remains constant for the duration of the model (key issue 3)

NICE

AE, adverse event; OCS, oral corticosteroid; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; SMR, standardised mortality ratio

Key issue 2: utility values (1/3)

Company did not use quality of life data from MANDARA in model

- MANDARA trial (n=140) used SF-36 to collect health state utility data; mapped to EQ-5D using mapping algorithm developed by Rowen et al. 2009
- Company did not use because it said results from MANDARA not consistent with insights from patient and clinical expert interviews:
  1. Minimal utility difference between remission and relapse – patients and clinical experts said HRQoL much better in remission than relapse (lower symptom burden, lower doses of medication)
  2. Refractory health state did not have lowest utility – patients and clinical experts said severe symptoms plus despair, anxiety, frustration at no remission for 6 months mean significant worsening of wellbeing
- Suggested there may be SF-36 limitations in EGPA
- Instead carried out 2 RWE studies: Adelphi DSP (n=177; 9 UK) and a UK-specific vignette study (300 people from general public and 21 with EGPA)
- Chose to use results from Adelphi DSP because it provided EQ-5D data for all 4 health states, had the larger number of people with EGPA, and mapped utilities using UK tariff
- More detail on RWE study results and methodology

EAG: agreed Adelphi DSP study best source of evidence for cost-effective analysis

Should utility values come from MANDARA or Adelphi DSP?

Adelphi DSP, Adelphi Real World Disease Specific Programme; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; RWE, real world evidence

Moderate impact on ICER

Key issue 2: utility values (2/3)

Company health state utility values and utility decrements used in the model

Health state utility values based on quality of life data from Adelphi DSP

Model health state	Utility value (SE)
Remission	[redacted]
Non-refractory	[redacted]
Refractory	[redacted]
Relapse	[redacted]

Utility decrements applied in the model for acute and chronic OCS-related adverse events

OCS-related chronic disease and acute events (based on Sullivan et al. 2011)	Utility decrement (SE)
Type 2 diabetes	-0.062 (0.0038)
Established cardiovascular disease	-0.087 (0.0155)
Osteoporosis	-0.042 (0.0063)
Adrenal insufficiency [redacted]	[redacted]
Cataract	-0.027 (0.0060)
Glaucoma	-0.028 (0.0063)
Peptic ulcer	-0.055 (0.0140)
Pneumonia	-0.079 (0.0420)
Renal impairment	-0.096 (0.0115)

NICE

Adelphi DSP: Adelphi Real World Disease Specific Programme; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroids; SE, standard error

Moderate impact on ICER

Key issue 2: utility values (3/3)

EAG base case increases values for refractory and relapse states

EAG comments

- Risk of overlap: [redacted] of 177 people in the Adelphi DSP study had organ damage (severe adverse event), which could be related to EGPA or treatment (including OCS)
- Model includes disutilities for OCS adverse events separately (see company's OCS sub-model); ideally utility estimates for each health state should not include OCS adverse events
- So could have underestimated utility in refractory and relapse states, assuming they have more OCS adverse events than non-refractory and remission states
- Adjusted base case to avoid double counting:
  - assumes:
    (1) organ damage more likely in refractory/relapse states than remission/non-refractory states
    (2) an acute or chronic OCS event in equal numbers for everyone in refractory/relapse states, none for remission/non-refractory states (simplifying assumption)
  - increased utility in refractory/relapse states by [redacted] (average disutility across all acute and chronic events)
  - exploratory scenario increased utility in refractory state only

Does the committee agree there is a risk of double counting adverse events? Does it agree with adjusting the utility for the refractory and relapse model health states?

NICE

Adelphi DSP: Adelphi Real World Disease Specific Programme; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroid

Moderate impact on ICER

Key issue 3: benralizumab discontinuation rate

Company and EAG use 5% per year discontinuation rate but uncertain

Background

- Response assessed at 52 weeks in model; response (BVAS=0 + OCS ≤4 mg/day) = stay on benralizumab for life; non-response = move to standard care, cannot switch back to benralizumab (see model stopping rule)
- Ongoing discontinuation rate unusually low in MANDARA (1.4% per year); other sources range 8% (MANDARA open-label extension) to 12% (in people with severe eosinophilic asthma, TA565) per year

Company

- Company assumption 5% discontinuation per year for benralizumab (conservative assumption – clinical experts said reflected UK clinical practice)
- Company explored higher discontinuation rate in scenario (7% per year)

EAG comments

- Substantial uncertainty over benralizumab discontinuation rate
- Used company assumption in base case but scenario analysis using other discontinuation rates:
  - 1.4% per year (MANDARA)
  - 8% per year (MANDARA open-label extension)

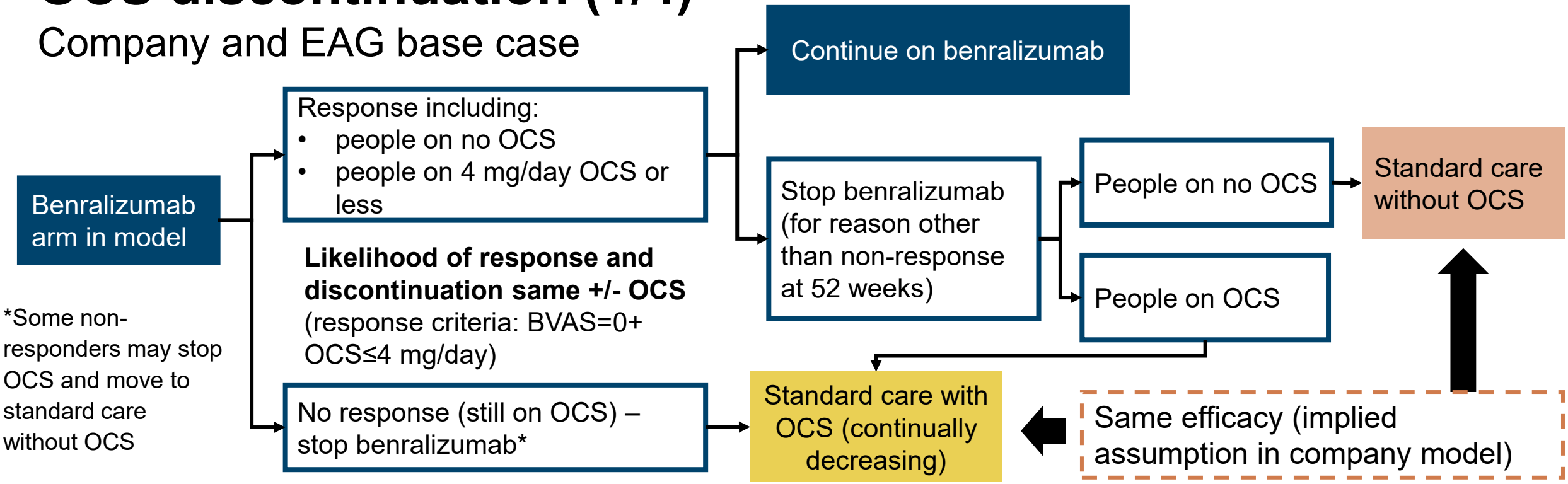
Which discontinuation rate for benralizumab is most plausible?

BVAS, Birmingham Vasculitis Activity Score; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IS, immunosuppressant; OCS, oral corticosteroid; TA, technology appraisal

Moderate impact on ICER

Key issue 4: relationship between benralizumab and OCS discontinuation (1/4)

Company and EAG base case



EAG comments

- Assumptions lead to: declining OCS over time in benralizumab arm; greater rate of benralizumab discontinuation = lower benralizumab ICER because standard care after benralizumab dominates standard care (effectiveness same but less OCS use = less AEs, greater QALYs, lower costs)
- OCS important part of standard care, with effect on remission, stable and relapse states
- Alternative assumptions of better efficacy for standard care with OCS in exploratory scenarios

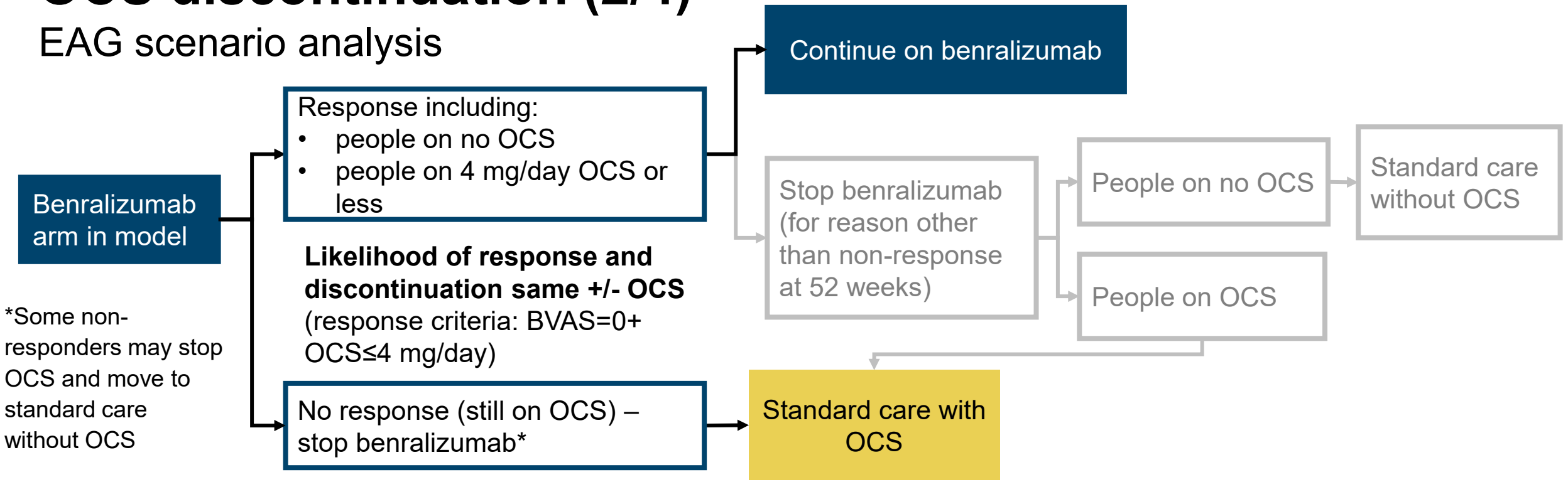
NICE Is it reasonable to assume the efficacy of standard care with OCS is the same as standard care without it?

AE, adverse event; BVAS, Birmingham Vasculitis Activity Score; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IS, immunosuppressant; OCS, oral corticosteroid; QALY, quality-adjusted life year

Moderate impact on ICER

Key issue 4: relationship between benralizumab and OCS discontinuation (2/4)

EAG scenario analysis



EAG exploratory scenario 6: everyone who stops OCS does not stop benralizumab

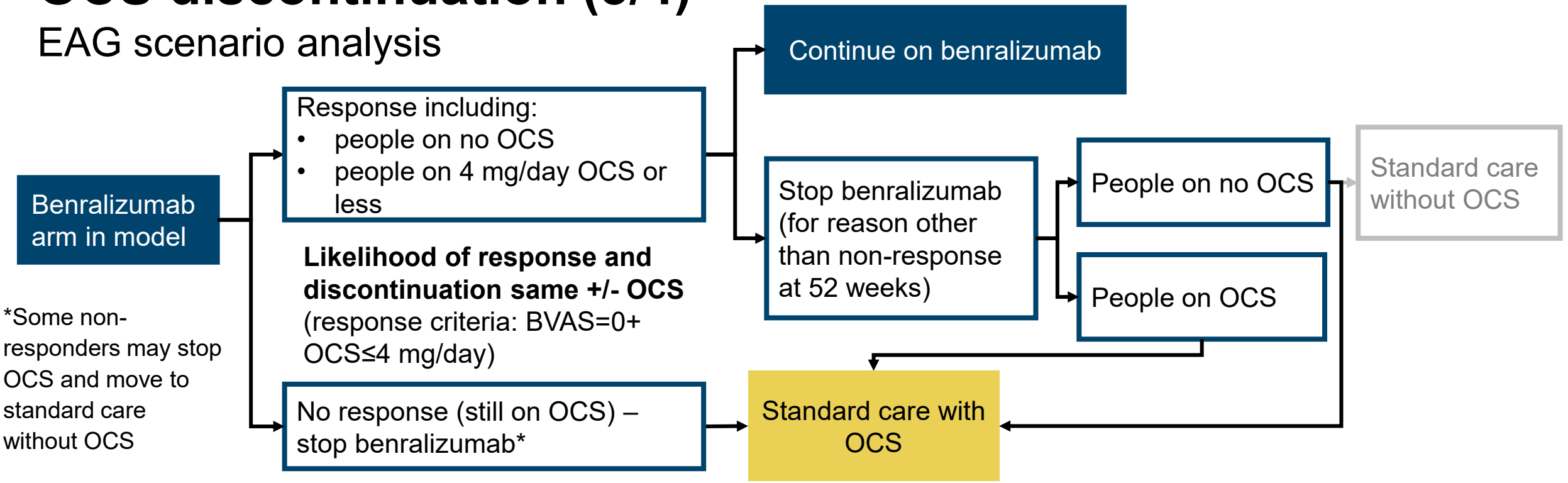
Is it reasonable to assume that if someone in the benralizumab arm stops OCS they will not then go on to stop benralizumab?

BVAS, Birmingham Vasculitis Activity Score; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IS, immunosuppressant; OCS, oral corticosteroid

Moderate impact on ICER

Key issue 4: relationship between benralizumab and OCS discontinuation (3/4)

EAG scenario analysis



EAG exploratory scenario 7: everyone who stops OCS on benralizumab starts again after stopping benralizumab

Is it reasonable to assume that if someone in the benralizumab arm stops OCS, then stops benralizumab, they will then restart OCS?

BVAS, Birmingham Vasculitis Activity Score; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IS, immunosuppressant; OCS, oral corticosteroid

Moderate impact on ICER

Key issue 4: relationship between benralizumab and OCS discontinuation (4/4)

Proportion of people having OCS in the benralizumab arm who stop benralizumab and move to standard care

[redacted]

EAG, external assessment group; ICER, incremental cost effectiveness ratio; OCS, oral corticosteroid

Small impact on ICER

Key issue 5: OCS discontinuation in benralizumab arm

OCS discontinuation rate: company assumes constant, EAG assumes declines linearly

Background

- Company model assumes OCS use:
  - constant over time at 86.2% in standard care arm (based on CPRD data)
  - discontinues by 38% per year indefinitely in benralizumab arm (derived from MANDARA)

EAG comments

- No evidence OCS discontinuation rate would continue beyond 1 year in benralizumab arm at same rate indefinitely
- Change in average dose over time in all patients in MANDARA suggests same rate of OCS discontinuation may not persist for ever
- Plausible that benefit of benralizumab would be in short period after start of treatment
- Possible that highest rate of OCS discontinuation within first 6 months, and falling to 0% by 1 year
- EAG base case: 38% annual discontinuation rate declines linearly to 0% at 5 years; scenario 0% at 1 year

[redacted]

Is it plausible that OCS use would discontinue at the same rate indefinitely in the benralizumab arm?

CPRD, clinical practice research datalink; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroid

Large impact on ICER

Key issue 6: no treatment waning

Company and EAG base cases assumed no treatment waning

Background

- Company did not incorporate treatment waning in the model
- Treatment effects assumed to stop when benralizumab stopped
- Effectiveness estimates that would be affected by waning include:
  - odds ratio of response (ITC estimate)
  - annualised relapse rate (ITC estimate)
  - reduction in % refractory stable patients (MANDARA trial)

Company

- Validated by company clinical experts
- Consistent with TA565 benralizumab for severe eosinophilic asthma (tech team note: consistency with precedent not required; evidence base varies between each evaluation)

EAG comments

- Retained assumption of no waning in EAG base case – has not suggested alternative; no scenarios presented
- Listed as key issue because any changes in assumption would significantly increase ICER

Is there any biological rationale for assuming a loss of treatment effect while on treatment? Is any loss of treatment effect already captured in treatment discontinuation?

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OCS, oral corticosteroid; TA, technology appraisal

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Treatment effectiveness	Bucher ITC	Bucher ITC
Treatment waning	None	None
Benralizumab discontinuation	5%	Same (scenarios at 1.4% and 8%)
OCS discontinuation in benralizumab arm	38% per year	Declines linearly from 38% in year 1 to 0% at year 5
Source of health state utilities	Adelphi DSP	Adelphi DSP but increased utility in refractory and relapse state to adjust for potential double counting of AEs
Source of health state costs	CPRD, eMIT, NHS reference costs 2021 to 2022, PSSRU 2023, National Cost Collection 2022–2023	Same

Adelphi DSP, Adelphi Real World Disease Specific Programme; AE, adverse event; CPRD, Clinical Practice Research Datalink; EAG, external assessment group; eMIT, electronic market information tool; ITC, indirect treatment comparison; OCS, oral corticosteroid; PSSRU, Personal Social Services Research Unit

Company base case results

Deterministic

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	26,092
Standard care	[redacted]	[redacted]	-	-	-

Probabilistic

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	27,166
Standard care	[redacted]	[redacted]	-	-	-

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Company and EAG base case results (deterministic)

Scenario	Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Company base case	Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	26,092
	Standard care	[redacted]	[redacted]	-	-	-
Increased utility in refractory and relapse states (key issue 2)	Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	30,520
	Standard care	[redacted]	[redacted]	-	-	-
Linear reduction in OCS discontinuation in benralizumab arm to 0% at year 5 (key issue 5)	Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	26,317
	Standard care	[redacted]	[redacted]	-	-	-
EAG base case	Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	30,798
	Standard care	[redacted]	[redacted]	-	-	-

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EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroid; QALY, quality-adjusted life year

EAG base case results

Deterministic

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	30,798
Standard care	[redacted]	[redacted]	-	-	-

Probabilistic

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Benralizumab plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	32,174
Standard care	[redacted]	[redacted]	-	-	-

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Uncaptured benefits

- The company highlighted the following potential extra benefits not captured in the QALY calculation:
  - In line with the England Rare Diseases Action Plan 2024:
    better access to effective treatment (first treatment specifically for EGPA)
    increased awareness of EGPA among health professionals – could improve diagnosis and treatment efficiency
  - Better quality of life as symptoms improve through remission and lower eosinophils, preventing further organ damage and slowing the disease
  - NHS cost savings by reducing need for treatment for organ damage
  - Expected that people will be able to self administer at home because of sustained remission
    convenient, saves time and money for patients
    savings for NHS
- The British Society for Rheumatology noted that reduced OCS use will improve health-related quality of life but that this would be difficult to quantify
- A clinical expert said that the conventional QALY calculation underestimates the long-term harm of OCS

Severity
No severity modifier applied

Managed access
No managed access proposal

OCS, oral corticosteroid; QALY, quality-adjusted life year

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

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- ✓ **Summary**

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Key issues

No	Issue	ICER impact
1	Generalisability to severe EGPA	Unknown
2	Utility values for refractory and relapse states	Moderate
3	Benralizumab discontinuation rate	Small
4	Relationship between benralizumab and OCS discontinuation	Moderate
5	OCS discontinuation	Small
6	No treatment waning	Large

OCS, oral corticosteroid

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

Supplementary appendix

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EGPA health states

Poorly characterised disease with 4 distinct health states

Health state	Definition
Remission	• Under control; no symptoms, or mild symptoms, such as such as blocked sinuses, numbness and tingling and fatigue (BVAS=0, plus ACQ-6 or SNOT-22 assessment) • Stable, low OCS dose (4 mg or less a day; definitions vary – some definitions allow up to 7 mg a day)
Non-refractory	• Not in remission but symptoms milder than in relapse • Reasonably well managed on stable doses of OCS • Condition mostly unchanged and may slowly improve
Refractory	• No remission in the past 6 months, not responding to treatment • High doses of OCS needed • Worse mental health than any other health state because of feelings of frustration, hopelessness, and despair, at not having any improvement for a long time
Relapse	• Significantly worsening symptoms (BVAS>0, worse ACQ-6 or SNOT-22 score) • Need for increased OCS dosage, or starting or increasing immunosuppressant treatment • Relapses contribute to irreversible and progressive organ damage, comorbidities

ACQ-6, Asthma Control Questionnaire; BVAS, Birmingham Vasculitis Activity Score; OCS, oral corticosteroid; SNOT-22, 22-item sino-nasal outcome test

Evidence in severe eosinophilic asthma

EAG comments

- Evidence from CALIMA trial (benralizumab as add-on treatment for severe, uncontrolled, eosinophilic asthma) suggests greater improvement in people with more severe disease
- CALIMA trial: people who had >3 exacerbations in the past year (that is, worse asthma at baseline) – trend towards greater effects of benralizumab treatment; post-hoc analysis showed 26% risk reduction for people with 2 previous exacerbations (vs placebo); 45% risk reduction for people with 3+ exacerbations

Annual asthma exacerbation rate ratio at 56 weeks in CALIMA

Exacerbations in past year (n)	Annual exacerbation rate ratio (95% CI)
2	0.78 (0.53, 1.14)
3	0.75 (0.45, 1.26)
≥4	0.35 (0.19, 0.65)

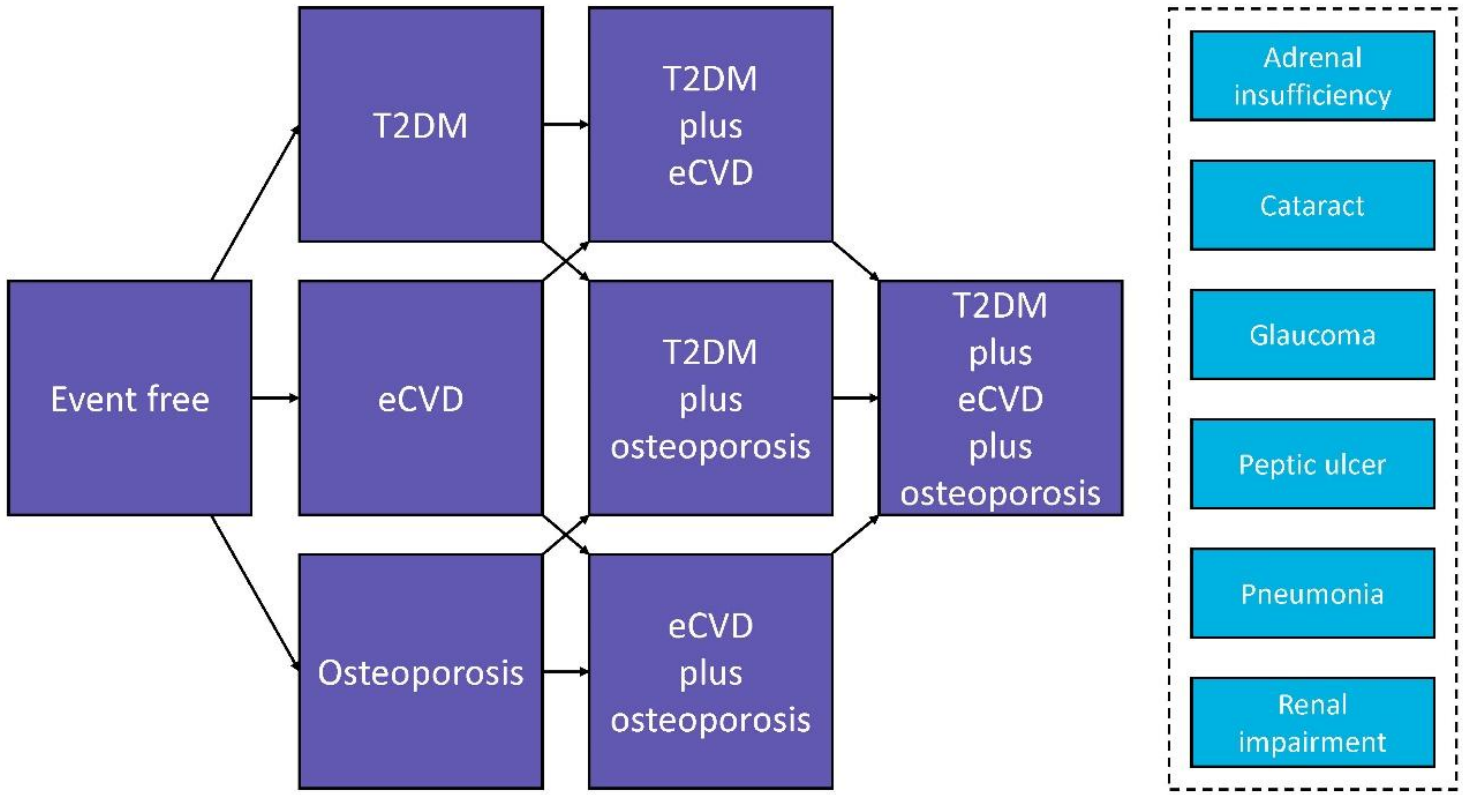
Key issue 1: generalisability to severe EGPA

CI, confidence interval; EAG, external assessment group; ICER, incremental cost-effectiveness ratio

Company's OCS sub-model

Company's model overview
Key issue 2: utility values

Captures impact of reducing OCS use on quality of life and NHS costs



- Model informed by Gibson et al. (2024); according to this study, use of OCS is associated with increased risk of AEs including acute clinical events and chronic comorbidities owing to cumulative lifetime OCS exposure
- Company: captures long-term impact of chronic conditions more effectively; noted that in previous technology appraisals on asthma (TA565 benralizumab, TA880 tezepelumab) AEs considered as acute events, which could underestimate the long-term impact of chronic conditions

AE, adverse event; eCVD, established cardiovascular disease; OCS, oral corticosteroids; T2DM, type 2 diabetes; TA, technology appraisal

Company rationale for SF-36 limitations in EGPA

Limitation	Rationale
SF-36 does not capture full symptom burden in EGPA	• Company clinical experts noted concerns about SF-36 not capturing patients' experience of living with EGPA, and challenged suitability of SF-36 for measuring QoL in EGPA • Recent systematic literature review on patient-reported outcomes in antibody-associated vasculitis reported no meaningful relationship between SF-36 and BVAS (Floyd et al. 2024) • SF-36 PCS may not accurately measure physical health status (Shroder et al. 2012); PCS domain includes physical functioning (impact on daily activities), impact on work because of impaired physical functioning and general health; particular importance in EGPA because disease has a significant impact on physical health of patients because of multisystem manifestations, damage to multiple organ systems and substantial fatigue; reduces peoples' ability to work and do; so SF-36 may under-estimate HRQoL impact of EGPA • The OMERACT Vasculitis Working Group has consistently highlighted concern that the SF-36 may not capture all important aspects of the EGPA (Robson et al. 2018)
Value lost mapping from SF-36 to EQ-5D	• Common for HRQoL data to lose predictive validity and any additional sensitivity when mapped to another preference-based measure (Rowen et al. 2009) • May have caused utility values for each health state to converge, losing sensitivity to the distinct HRQoL impacts of each health state

Key issue 2: utility values for refractory and relapse states

BVAS: Birmingham Vasculitis Activity Score; HRQoL: health-related quality of life; OCS: oral corticosteroids; OMERACT: Outcome Measures in Rheumatology; PCS: physical component summary;

Adelphi DSP and vignette study methodology

Study	Description and methodology
Adelphi DSP	• Cross-sectional physician and patient survey done in France, Germany, Italy, Spain, UK and US between July to December 2023 • Disease severity based on physician's definition and patients completed EQ-5D-5L questionnaires; 177 patients (9 from UK) completed questionnaire • Utility scores generated from EQ-5D-5L cross walked to EQ-5D-3L using UK tariff
UK vignette	• Vignette descriptions developed based on literature review, analysis of patient-level data from MANDARA, and interviews with 8 patients with EGPA, 4 clinical experts who have treated patients with EGPA and 1 HRQoL expert experienced with EGPA • Valuation of vignettes done with 300 people without EGPA and 21 people with EGPA (company notes that 21 people with EGPA is a substantial number, given the rarity of the disease (70 patients in the benralizumab arm of the MANDARA trial) • Participants completed EQ-5D-5L questionnaires, and utility scores generated from EQ-5D-5L were cross-walked to EQ-5D-3L using UK tariff • Vignettes were developed and carried out in line with NICE DSU guidance

Key issue 2: utility values for refractory and relapse states

HRQoL, health-related quality of life; NICE DSU, NICE Decision Support Unit

Health utilities from MANDARA and real world evidence studies

Health state	MANDARA: SF-36 mapped to EQ-5D	IPD retrospectively analysed from MANDARA: SF-36 mapped to EQ-5D	Adelphi DSP	Vignette: general population valuation	Vignette: patient valuation
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	-	-	-	-
Non-refractory	-	[redacted]	[redacted]	[redacted]	[redacted]
Refractory	-	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue 2: utility values for refractory and relapse states

Adelphi DSP, Adelphi Real World Disease Specific Programme; IPD, individual patient data