

Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

**Benralizumab for treating relapsing or refractory eosinophilic granulomatosis
with polyangiitis [ID6266]**

Contents:

The following documents are made available to stakeholders:

The [final scope and final stakeholder list](#) are available on the NICE website.

- 1. Company submission summary** from AstraZeneca
- 2. Company summary of information for patients (SIP)** from AstraZeneca
- 3. Clarification questions and company responses**
- 4. Patient group, professional group and NHS organisation submissions**
from:
 - a. Vasculitis UK
 - b. Association of Respiratory Nurse Specialists
 - c. British Society for Rheumatology
 - d. UK Kidney Association
 - e. UK and Ireland Vasculitis Rare Disease Group
- 5. Expert personal perspectives** from:
 - a. Clinical Expert, nominated by AstraZeneca
 - b. Patient Expert, nominated by Vasculitis UK
- 6. External Assessment Report** prepared by Newcastle NIHR TAR Team,
Newcastle University
- 7. External Assessment Report – factual accuracy check**

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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Benralizumab for treating relapsing or
refractory eosinophilic granulomatosis with
polyangiitis (ID6266)**

Document B

Company evidence submission

November 2024

File name	Version	Contains confidential information	Date
ID6266 Benralizumab in EGPA Document B_30Apr25_[NoCON]	1.1	No	30/04/2025

Contents

Contents	2
Tables.....	2
Figures	4
Abbreviations	5
B.1 Decision problem, description of the technology and clinical care pathway.....	9
B.1.1 Decision problem.....	9
B.1.2 Description of the technology being evaluated	13
B.1.3 Health condition and position of the technology in the treatment pathway	15
B.1.4 Equality considerations	27
B.2 Clinical effectiveness	28
B.2.1 Identification and selection of relevant studies	28
B.2.2 List of relevant clinical effectiveness evidence	28
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence	30
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	38
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence	40
B.2.6 Clinical effectiveness results of the relevant trials	42
B.2.7 Subgroup analysis.....	52
B.2.8 Meta-analysis	52
B.2.9 Indirect treatment comparison.....	52
B.2.10 Adverse reactions.....	55
B.2.11 Ongoing studies	63
B.2.12 Interpretation of clinical effectiveness and safety evidence.....	63
B.3 Cost effectiveness	66
B.3.1 Published cost-effectiveness studies	66
B.3.2 Economic analysis.....	67
B.3.3 Clinical parameters and variables	81
B.3.4 Measurement and valuation of health effects	95
B.3.5 Cost and healthcare resource use identification, measurement and valuation	103
B.3.6 Severity.....	107
B.3.7 Managed access proposal	108
B.3.8 Summary of base-case analysis inputs and assumptions.....	108
B.3.9 Base-case results.....	116
B.3.10 Exploring uncertainty.....	118
B.3.11 Subgroup analysis.....	123
B.3.12 Benefits not captured in the QALY calculation	123
B.3.13 Validation.....	124
B.3.14 Summary	124
References	127

Tables

Table 1: The decision problem for this submission	10
Table 2: Technology being appraised.....	13
Table 3: EGPA health states.....	18
Table 4: Clinical effectiveness evidence.....	29

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 5: Summary of methodology for the MANDARA trial	31
Table 6: Baseline patient and disease characteristics in the MANDARA trial	36
Table 7: Description of populations for analyses.....	38
Table 8: Statistical methods for the primary analysis in MANDARA	39
Table 9: Critical appraisal of clinical effectiveness evidence	40
Table 10: Proportion of patients with remission at both Weeks 36 and 48 across both treatment arms (full analysis set)	42
Table 11: Proportion of patients with main remission within the first 24 weeks and remaining in remission for the remainder of the DB period until Week 52 (full analysis set).....	44
Table 12: Time to first relapse and time to first major relapse, Cox-proportional hazard model (full analysis set)	45
Table 13: Annualised relapse rate and major relapse rate across treatment arms (full analysis set)	47
Table 14: Proportion of patients with reduction from baseline in average daily dose of OCS during Weeks 48 through 52 (full analysis set).....	49
Table 15: The change from baseline to Week 52 in absolute eosinophil count (full analysis set).....	50
Table 16: BVAS response rate (full analysis set)	51
Table 17: Spirometry parameters and change from baseline over time (full analysis set)	51
Table 18: Inputs used in Bucher ITC analysis	54
Table 19: Summary of Bucher ITC Results	54
Table 20: The duration of exposure to IP during the DB period (safety analysis set).....	56
Table 21: The duration of exposure to IP during the OLE period (safety analysis set)	56
Table 22: AEs in any category during the DB and OLE period (safety analysis set).....	57
Table 23: AEs in any category during the DB period (safety analysis set)	57
Table 24: AEs in any category during the OLE period (safety analysis set).....	58
Table 25: Most common AEs in the DB period, with PT frequency of >3% (safety analysis set). 58	
Table 26: Most common treatment-related AEs in the DB period, with PT frequency of ≥2 patients in either group (safety analysis set)	60
Table 27: SAEs during the DB period (safety analysis set)	61
Table 28: AEs leading to discontinuation of IP during the DB period (safety analysis set)	62
Table 29: Features of the base case economic analysis	67
Table 30: Overview of workstreams conducted to deepen understanding of EGPA evolution	69
Table 31: EGPA health state definitions in the cost-effectiveness analysis.....	71
Table 32: Comparator treatments in the cost-effectiveness analysis	80
Table 33: Summary of clinical data sources informing the cost-effectiveness analysis	82
Table 34: Inputs for baseline characteristics	84
Table 35: Inputs for comorbidities at baseline	84
Table 36: Inputs for treatment response with benralizumab	85
Table 37: Transition probabilities in the benralizumab arm.....	86
Table 38: Relative efficacy of benralizumab versus SoC	86
Table 39: Transition probabilities in the SoC arm.....	87
Table 40: Inputs for mortality	89
Table 41: Relevant treatment discontinuation rates from alternative sources	90
Table 42: Inputs for benralizumab discontinuation used in the base case analysis	90
Table 43: Inputs for OCS discontinuation	91
Table 44: Inputs for OCS dose for each health state	91
Table 45: Inputs for general population rate of chronic disease onset	92
Table 46: Inputs for the effects of OCS on chronic disease onset.....	93
Table 47: Inputs for chronic disease progression.....	93

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 48: Inputs for general population rate of acute event onset.....	94
Table 49: Inputs for the effects of OCS use on acute event onset.....	94
Table 50: Results of SF-36 mapped to EQ-5D.....	97
Table 51: Rationale for SF-36 limitations	97
Table 52: Adelphi DSP and vignette study methodology	99
Table 53: Adelphi DSP and vignette study results	100
Table 54: Interpretation of Adelphi DSP and vignette study results.....	100
Table 55: Utility decrements for chronic OCS-related comorbidities and acute events.....	101
Table 56: Summary of utility values for the cost-effectiveness analysis	102
Table 57: Acquisition costs for benralizumab	103
Table 58: Acquisition costs for SoC.....	105
Table 59: Frequency of healthcare resource use, by health state, per patient per year for disease management	105
Table 60: Unit costs for disease management	106
Table 61: Costs for chronic OCS-related comorbidities and acute events	107
Table 62: Summary of QALY shortfall analysis	107
Table 63: Summary of base case inputs	108
Table 64: Assumptions in the economic model	113
Table 65: Deterministic base-case results for benralizumab versus SoC (with PAS)	117
Table 66: Probabilistic base-case results for benralizumab versus SoC (with PAS).....	117
Table 67: Results of the scenario analyses (with PAS; probabilistic)	121

Figures

Figure 1: Mechanism of action of benralizumab.....	13
Figure 2: The role of eosinophils in the pathogenesis of EGPA.....	17
Figure 3: The organ systems impacted by EGPA	20
Figure 4: The current EGPA treatment pathway	24
Figure 5: Potential future clinical care pathway for patients with EGPA	26
Figure 6: MANDARA study design	30
Figure 7: Patient enrolment and randomisation in MANDARA	38
Figure 8: Time to first relapse – Kaplan Meier plot (full analysis set).....	46
Figure 9: Cost-effectiveness model structure	72
Figure 10: OCS sub-model structure.....	75
Figure 11: How the OCS sub-model was incorporated into the overarching economic model	76
Figure 12: Model structure parameterisation, by treatment arm – benralizumab arm	77
Figure 13: Model structure parameterisation, by treatment arm – SoC arm.....	78
Figure 14: Assessing response to benralizumab	85
Figure 15: Informing the proportion of patients in refractory sub-state by treatment arm.....	89
Figure 16: ICER convergence plot for benralizumab versus SoC (with PAS)	118
Figure 17: Probabilistic cost-effectiveness plane for benralizumab versus SoC (with PAS)	119
Figure 18: Cost-effectiveness acceptability curve for benralizumab versus SoC (with PAS).....	119
Figure 19: DSA tornado diagram for ICER for benralizumab versus SoC (with PAS).....	120

Abbreviations

Abbreviation	Definition
µL	Microlitre
µmol	Micromolar
A&E	Accident and emergency
AAV	ANCA-associated vasculitis
ACQ-6	Asthma control questionnaire
ACR	American College of Rheumatology
ADCC	Antibody-dependent cell-mediated cellular cytotoxicity
AE	Adverse event
APC	Admitted patient care
ARR	Annualised relapse rate
ANCA	Anti-neutrophil cytoplasmic antibody
AZA	Azathioprine
BD	Bronchodilator
BEC	Blood eosinophil count
BMI	Body mass index
BNF	British National Formulary
BSR	British Society for Rheumatology
BTS	British Thoracic Society
BVAS	Birmingham Vasculitis Activity Score
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CYC	Cyclophosphamide
DB	Double blind
dL	Decilitre
DSA	Deterministic sensitivity analysis
DSP	Disease specific programme
DSU	Decision support unit
eCRF	Electronic case report form
eCVD	Established cardiovascular disease
ED	Emergency department
EGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
eMIT	Electronic marketing information tool
ENT	Ear, nose and throat
EULAR	European Alliance of Associations for Rheumatology
Fab	Fragment of antigen binding
Fc	Fragment crystallisable region

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

FCγRIIIα	FCγ receptor alpha
FVC	Forced vital capacity
FEV1	Forced expiratory volume in 1 second
GI	Gastrointestinal
GINA	Global Initiative for Asthma
GP	General practitioner
GPA	Granulomatosis with polyangiitis
GRAD	Global retention and disposal schedule
HCP	Healthcare professional
HCRU	Healthcare resource use
HSE	Health Survey for England
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
IEC	Independent ethics committee
ICER	Incremental cost-effectiveness ratio
ICH GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good clinical practice
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
ILC2	Type 2 innate lymphoid cells
IM	Intramuscular
IP	Investigational product
IPD	Individual patient data
IPQ	Illness perception questionnaire
IRB	Institutional review board
IS	Immunosuppressants
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
L	Litre
LY	Life years
MA	Marketing authorisation
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
max	Maximum
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
min	Minimum
MoA	Mechanism of action
MPA	Microscopic polyangiitis

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

MTX	Methotrexate
N/A	Not applicable
NHB	Net health benefit
NHS	National Health Service
NI	Non-inferiority
NICE	National Institute for Health and Care Excellence
NK	Natural killer
OCS	Oral corticosteroids
OLE	Open-label extension
ONS	Office for National Statistics
OP	Outpatient
OPCRD	Optimum Patient Care Research Database
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
PAS	Patient access scheme
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
PY	Patient-years
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Rate ratio
RTX	Rituximab
RWE	Real-world evidence
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEA	Severe eosinophilic asthma
SLR	Systematic literature review
SF-36	Short Form 36-Item Health Survey
SF-36v2	Short Form 36-Item Health Survey - Version 2
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SNOT-22	22-Item Sino-Nasal Outcome Test

SoC	Standard of care
SOC	System organ class
T2DM	Type-2 diabetes mellitus
TA	Technology appraisal
Th2	Type 2 T-helper cells
TSD	Technical support documents
UK	United Kingdom
US	United States
VDI	Vasculitis Damage Index
wk	Week
WPAI-GH	Work productivity and activity impairment Questionnaire - General Health
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

This single technology appraisal evaluates the clinical and cost effectiveness of benralizumab as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) receiving oral corticosteroids (OCS) with or without stable immunosuppressive (IS) therapy. The anticipated marketing authorisation wording is: "[REDACTED]

[REDACTED]"

The decision problem addressed in this submission, compared with the final scope issued by NICE, is summarised in Table 1.

Table 1: The decision problem for this submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy	In line with final scope	N/A
Intervention	Benralizumab	In line with final scope	Throughout the submission, benralizumab should be considered as benralizumab + SoC, where SoC is defined as OCS with or without stable IS. This aligns with the use of benralizumab in MANDARA ¹
Comparator(s)	Established clinical management without benralizumab, including: • OCS (do not currently have a marketing authorisation in the UK for this indication) • CYC (does not currently have a marketing authorisation in the UK for this indication) • Other IS agents (do not currently have a marketing authorisation in the UK for this indication) • RTX (does not currently have a marketing authorisation in the UK for this indication)	Established clinical management, henceforth referred to as “SoC”, in UK clinical practice, including: • OCS • Other IS agents (e.g. methotrexate, azathioprine, mycophenolate mofetil)	The appropriate comparator for this submission is a weighted average of the most used agents for the management of EGPA in UK clinical practice. Analysis of UK prescription data and clinical expert opinion indicate that the most used agents to induce and maintain remission for EGPA are OCS and IS (e.g. methotrexate, azathioprine and mycophenolate mofetil) and therefore, these are considered to form SoC in the UK.^{2,3} The treatment distribution was informed by CPRD data, which was validated by clinical expert opinion as being representative of UK clinical practice²⁻⁴ AstraZeneca does not believe that CYC and RTX are appropriate comparators for this submission, considering the different positioning of these agents in the EGPA treatment pathway, compared to the anticipated positioning of benralizumab. Specifically: • Clinical guidelines and clinical expert opinion indicate that CYC and RTX are predominantly restricted to the treatment of patients with severe EGPA, defined as life- or organ-threatening EGPA.³ Patients with life- or organ-threatening EGPA manifestations were excluded from MANDARA and therefore are not addressed within this submission

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

			- Furthermore, patients with previous CYC treatment (oral and IV use within two and three weeks of baseline [Visit 2], respectively) and patients with previous RTX treatment (within six months of study enrolment [Visit 1])^a were also excluded from MANDARA, meaning that these agents are not appropriate comparators for the purpose of this submission Additionally, CYC and RTX are not routinely used in UK clinical practice: - CYC is associated with concerns of organ-threatening toxicity and affects fertility, which are worsened by cumulative doses, so clinicians are keen to restrict use to patients with severe EGPA⁵ - As per the NHS England Clinical commissioning policy, and as substantiated by feedback from clinicians, RTX is not commonly used, and its use is likely to be greatly limited in UK clinical practice, given the restricted criteria for commissioning⁶ - An analysis of CPRD data from 486 patients with EGPA, conducted in 2024, identified that CYC was only used in 2.7% of patients in England and RTX in only 1% of patients⁴ - Clinical experts further validated that CYC was restricted to treating severe patients and RTX was only sparingly used in UK clinical practice, and does not form part of UK SoC³
Outcomes	The outcome measures to be considered include: - Mortality - Remission rates - Total accrued duration of remission - Time to first relapse	In line with final scope	N/A

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	• Number of relapses • Reduction/cessation in systemic steroid use • Use of IS • Vasculitis activity scores • Pulmonary function • AEs of treatment • HRQoL		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account	In line with final scope and reference case	N/A

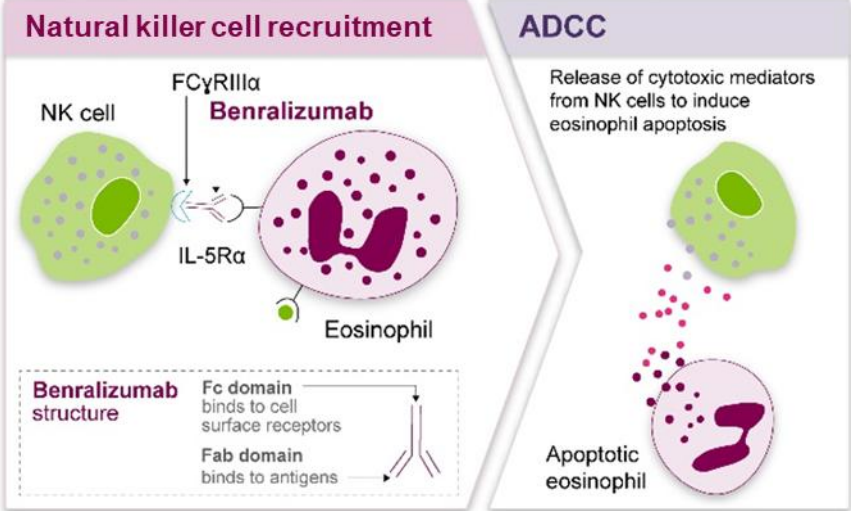
Footnotes: ^a Patients must have also shown recovery of peripheral B-cell count to within the normal range

Abbreviations: AE: adverse event; CPRD: Clinical Practice Research Datalink; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; HRQoL: health related quality of life; IS: immunosuppressant; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OCS: oral corticosteroids; PSS: Personal Social Services; RTX: rituximab; SoC: standard of care; UK: United Kingdom

B.1.2 Description of the technology being evaluated

A description of the technology being appraised, benralizumab (FASENRA®), is provided in Table 2. The Summary of Product Characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Benralizumab (FASENRA®)
Mechanism of action	Benralizumab is a humanised monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of IL-5Rα which is expressed on eosinophils and basophils.^{1,7} The binding of benralizumab to the IL-5 receptor blocks the binding of the IL-5 ligand, inhibiting eosinophil activation. In an in-vitro setting, the absence of fucose (a sugar molecule) in the Fc domain of benralizumab facilitates binding to FcγRIII receptors on immune effector cells, such as NK cells, leading to apoptosis of eosinophils through ADCC (Figure 1).^{8, 9, 10} Apoptosis of eosinophils results in reduced inflammation and formation of eosinophilic granulomas, reducing damage to organ systems¹¹ Figure 1: Mechanism of action of benralizumab  Source: This figure has been adapted from: Dagher <i>et al</i> European Respiratory Journal, 2022;⁸ Kolbeck <i>et al</i> Journal of Allergy and Clinical Immunology, 2010⁹
Marketing authorisation/CE mark status	A MA application was submitted to the EMA in November 2023. A positive opinion from the CHMP was received in September 2024 with MA approval from the EMA received in October 2024. A MA application was submitted to the MHRA for benralizumab via [REDACTED], in [REDACTED], with the [REDACTED]. Marketing authorisation is expected from the MHRA in [REDACTED].
Indications and any restriction(s) as described in the SmPC	Relevant to this submission, benralizumab is anticipated to be indicated [REDACTED] In addition, benralizumab received marketing authorisation from the MHRA in January 2018 as an add-on maintenance treatment in adult patients with

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β -agonists
Method of administration and dosage	Relevant to this indication, benralizumab will be administered as a 30 mg dose, Q4W by SC injection (FASENRA Pen®)
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	The list price of benralizumab is £1,955 per 30 mg pre-filled pen
Patient access scheme (if applicable)	A simple discount PAS is in place for the funding of the current benralizumab indication (severe eosinophilic asthma) via baseline commissioning. This existing discount of ■% will apply to the indication covered by this submission, making the price of a 30 mg pre-filled pen £■

Abbreviations: ADCC: antibody-dependent cell-mediated cellular cytotoxicity; BNF: British National Formulary; CHMP: Committee for Medicinal Products for Human Use; EGPA: eosinophilic granulomatosis with polyangiitis; EMA: European Medicines Agency; Fab: fragment of antigen binding; Fc: fragment crystallisable region; FC γ RIII α : FC γ receptor alpha; IL-5R α : interleukin-5 receptor alpha; MA: marketing authorisation; MHRA: Medicines and Healthcare products Regulatory Agency; NK: natural killer cell; PAS: patient access scheme; SC: subcutaneous; SmPC: summary of product characteristics; Q4W: every 4 weeks

Source: FASENRA SmPC;¹² BNF;¹³ AstraZeneca. Data on File. Draft benralizumab SmPC¹⁴

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

Disease overview and burden

- EGPA is a rare, autoimmune, inflammatory condition, affecting approximately 2,600 people in the UK^{15, 16}
- EGPA is a hypereosinophilic disorder, characterised by elevated circulating and tissue eosinophils, which cause inflammation of small and medium-sized blood vessels, resulting in restricted blood flow and subsequent damage to multiple organs^{17, 18}
- EGPA manifests across multiple organ systems, with significant symptom burden.¹⁸⁻²⁰ Diagnosis is challenging, owing to symptom overlap with other diseases²¹
- Severe, multi-system manifestations and organ damage have a considerable negative impact on patients' health-related quality of life (HRQoL) due to substantial fatigue, functional impairment and limitations in daily activities including a reduced ability to work.^{22, 23} Additionally, continuous cycles of adequate disease control alternating with symptom recurrence contribute to patients feeling low, anxious and frustrated about their condition.^{22, 24} EGPA also negatively impacts carers' mental health and ability to remain employed²⁵
- EGPA is characterised by four distinct health states:
 - Remission: controlled disease, with no or mild symptoms^{3, 26}
 - Relapse: recurrence of EGPA symptoms or requirement for increased OCS dose^{2, 21, 26-28}
 - Non-refractory disease: not remission nor relapse, but stable or tapered OCS dose, that patients derive clinically meaningful benefit from
 - Refractory disease: no remission in the prior 6 months, severe symptoms and a requirement for high OCS doses, with an amplified negative impact on mental health due to feelings of frustration, hopelessness and despair resulting from patients experiencing a lack of improvement over a prolonged period of time
- EGPA is associated with a 5-year mortality of 17.6%, 2.3 times higher than observed in a matched control population²⁹

Clinical care pathway

- There are currently no reimbursed treatment options for EGPA in the UK.³⁰ Standard of care (SoC) in the UK comprises of high-dose OCS and IS (e.g. methotrexate, mycophenolate mofetil and azathioprine) prescribed off-label to reduce inflammation^{21, 26-28, 30}

Unmet need

- OCS and IS are sub-optimal treatment options as there is substantial evidence associating OCS use with acute and chronic adverse events (AEs),³¹⁻³³ while IS are associated with toxicities, including hepatotoxicity.^{21, 26-28, 32, 33} Additionally, OCS and IS fail to adequately control the disease³³⁻³⁵
- Consequently, there is a high unmet need for novel targeted therapies which provide adequate and durable disease control and enable a reduction in OCS exposure

Proposed positioning of benralizumab

- Benralizumab is anticipated to be an add-on to SoC for relapsing or refractory EGPA
- Benralizumab would address the unmet need and allow patients to benefit from an innovative therapy which offers durable remission, and enables a reduction in OCS-dependence and the incidence of OCS-related AEs

B.1.3.1 Disease overview

Introduction to EGPA

EGPA is a rare, autoimmune vasculitis caused by hypereosinophilia which leads to inflammation-induced damage to organs

EGPA, previously known as Churg-Strauss syndrome, is a rare, autoimmune vasculitis characterised by high levels of circulating and tissue eosinophils (hypereosinophilia) which drive necrotising inflammation of small and medium-sized blood vessels.¹⁷ Eosinophils are specialised white blood cells that are involved in the host defence against infection. EGPA presents with a variety of clinical manifestations that can impact multiple organ systems simultaneously, resulting in cumulative, chronic organ damage.¹⁸ Commonly affected organ systems include cardiac, gastrointestinal (GI), pulmonary, cutaneous and renal, with the most common manifestations including asthma, myocarditis (inflammation of the heart), mononeuritis multiplex (peripheral nerve disorders) and ear, nose and throat (ENT) infections.¹⁸

Epidemiology

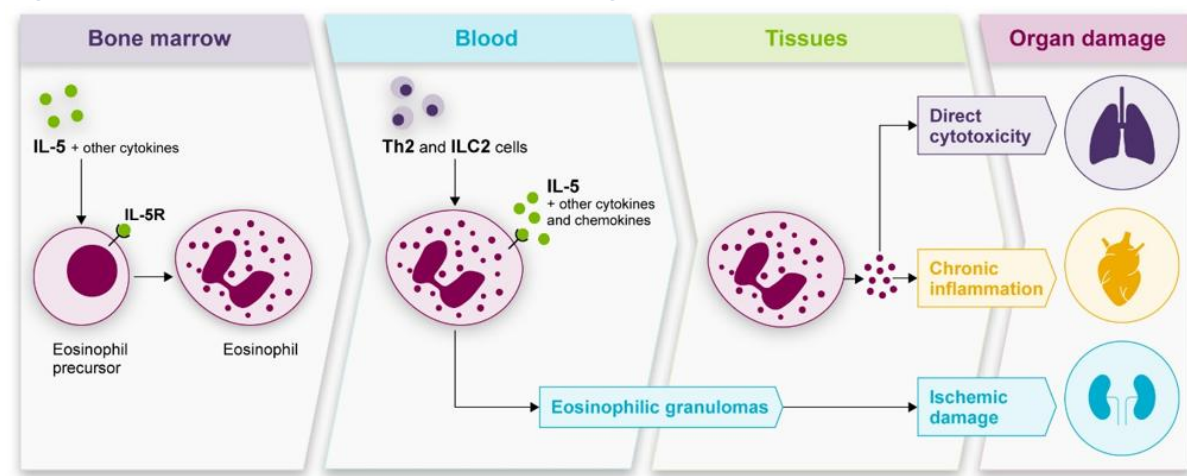
EGPA is a rare and poorly characterised disease with limited epidemiology evidence available. The most relevant UK-specific source identified in literature following a targeted search reported that EGPA affects approximately 45.6 per million people (children and adults) in the UK.¹⁵ Based on this estimated prevalence, AstraZeneca anticipates that EGPA affects approximately 2,600 people in England in 2024 (assuming ONS mid-2023 estimate for the population of England of 57,690,323).^{15, 16} The disease affects men and women equally, and is typically diagnosed in middle age, with a median age at diagnosis of 57.4 years.¹⁵ EGPA rarely affects children (<18 years) with a prevalence of 0.4 per million children, compared to 56.8 per million in adults (≥18 years).¹⁵

Pathogenesis

EGPA is characterised by high levels of circulating and tissue eosinophils, which release cytokines and chemokines (small proteins that act as signalling molecules) causing necrotising inflammation of small or medium-sized blood vessels.^{17, 36} Blood eosinophil counts (BECs) normally range from 50–500 cells/μL in healthy people; however, they are elevated in the blood and tissues of patients with EGPA (mean BEC of 1,385.5 cells/μL), and can increase to levels ten times greater than in people without EGPA.^{11, 15}

The proliferation and migration of eosinophils from the bone marrow into circulation is primarily regulated by IL-5, which binds to the receptor α subunit (interleukin-5Rα) expressed on eosinophils (Figure 2).^{1, 11} Type 2 T helper cells (Th2) and type 2 innate lymphoid cells (ILC2s) produce cytokines to promote eosinophilic growth and activation. Once in the circulatory system, eosinophils move into vessel walls and extensively infiltrate tissues, mediated by IL-5 and other cytokines and chemokines, leading to eosinophilic granuloma (white blood cell cluster) formation.¹⁷ These granulomas cause ischaemic organ damage (organ damage due to restricted blood supply).^{11, 37} Furthermore, the increased eosinophils and associated chronic inflammation can cause direct and indirect tissue damage.

Figure 2: The role of eosinophils in the pathogenesis of EGPA



Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IL-5: interleukin-5; IL-5R: interleukin-5 receptor; ILC2: type 2 innate lymphoid cells; Th2: type 2 T helper cells

Source: AstraZeneca GVP

Disease course

There are four distinct health states: remission, non-refractory, refractory and relapse.

EGPA is a poorly characterised rare disease, given the limited innovation and research in this space to date, resulting in a scarcity of literature to help inform the evolution of the disease. Consequently, extensive work was undertaken by AstraZeneca to deepen the understanding of the disease in support of this submission. This included systematic literature reviews, an advisory board with patients and extensive consultation with clinical experts.^{3, 38} A separate workstream was also undertaken which included consultation with patients with EGPA through eight in-depth interviews and with clinical experts through four in-depth interviews, as part of defining the health state descriptions for the purpose of conducting a UK-specific vignette study.³⁹ Any insights gathered from the advisory board and interviews with patients are henceforth referred to as “patient insights”. Further information on the work undertaken is provided in Section B.3.2.2. Collectively, EGPA is best described by four health states, as outlined below, with patients broadly experiencing a relapsing and remitting disease course based on the occurrence of clinical signs and symptoms and OCS dose required to control the disease (Table 3).

Remission is defined as the disease being “under control”, requiring low doses of medication. Patients experience no symptoms or some mild symptoms, such as blocked sinuses, numbness and tingling and fatigue.^{3, 26}

Relapse is defined as the recurrence of EGPA signs and symptoms, or the requirement for increased doses of medication, after a period of remission.²⁶ Patients in relapse experience more severe symptoms than those in remission, including severe fatigue, loss of sensation in limbs, weight changes and skin problems.^{2, 21, 26-28} Relapses contribute to irreversible and progressive organ damage, development of comorbidities, the need for increased dosages of OCS (associated with severe AEs and toxicity, as described in Section B.1.3.4), poor HRQoL (as described in ‘Impact on patient and carer quality of life’) and increased mortality compared with the other health states.^{2, 21, 26-28}

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Some patients are considered to be in neither remission nor relapse and are characterised by a spectrum of disease control that, according to clinical expert opinion, can broadly be categorised into two sub-states with different clinical profiles: non-refractory and refractory disease.³

- On the “better” end of the spectrum, patients with **non-refractory** disease can achieve a stable or tapered OCS dose and experience clinically meaningful benefit compared with refractory disease, given that OCS dose reduction is a key treatment goal in EGPA
- On the “worse” end of the spectrum, the **refractory** health state includes patients without remission in the prior six months and is characterised by severe symptoms, and a requirement for high doses of oral corticosteroids.²⁶⁻²⁸ In addition, patients with refractory disease experience an amplified negative impact on mental health due to feelings of frustration, hopelessness and despair resulting from them experiencing a lack of improvement over a prolonged period of time (‘Impact on patient and carer quality of life’)³⁹

Table 3: EGPA health states

Health state	Definition
Remission ²⁶	• Absence of or mild clinical signs or symptoms attributable to active disease, including asthma and ENT manifestations (BVAS = 0, combined with assessment with ACQ-6 or SNOT-22) • Stable OCS dose $\leq 4\text{--}7.5$ mg daily (definitions vary)
Non-refractory ³	• Stable OCS dose or tapered OCS dose related to EGPA
Refractory ³	• Not having achieved remission at any time in the prior six months, and not responding to treatment • Amplified negative impact on mental health than any other health state, due to feelings of frustration, hopelessness, and despair, having not experienced improvement over a prolonged period of time
Relapse ²⁶	• Recurrence of clinical signs or symptoms attributable to active disease following a period of remission (assessed with BVAS, ACQ-6 or SNOT-22) • The need for an increase in the OCS dosage or the initiation of or an increase in an IS should also be considered a relapse

Abbreviations: ACQ-6: Asthma Control Questionnaire; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose and throat; IS: immunosuppressants; OCS: oral corticosteroids; SNOT-22: 22-item sino-nasal outcome test

Further detail on how these health states were incorporated in the economic model to capture the evolution of the disease is provided in Section B.3.2.2. Given data limitations, it was not possible to implement the refractory and non-refractory health states as individual health states. Therefore, these were modelled as sub-states within a ‘stable disease’ health state.

Diagnosis

The multitude of symptoms and the considerable overlap between EGPA symptoms and those of other diseases create a challenge in the diagnosis of EGPA. Additionally, the rarity of the disease, the lack of specialist expertise, a lack of innovation and research in EGPA and no updates to management guidelines in recent years, all also contribute to difficulties in diagnosis.²¹ Consequently, the mean time from onset of symptoms to EGPA diagnosis has been reported as 7.1–11.8 years.^{38, 40} This delay in diagnosis can result in greater disease severity, progression and disease burden as patients present with a broader range of manifestations and associated symptoms contributing to organ damage, requiring additional OCS and IS in an attempt to induce remission.²⁰ Complex diagnoses lead to repeated hospital visits and worsening

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

symptoms over time. This can leave patients feeling anxious, depressed, confused and frustrated as they struggle with the uncertainty of their health.²² Late diagnosis also increases the economic burden on the NHS as greater levels of specialist treatment and monitoring are required for progressed disease.

Mortality

Mortality rates remain significantly higher in individuals with EGPA compared to matched control populations.^{38, 41, 42} An analysis of real-world CPRD data in England reported that patients with EGPA had a 5-year mortality rate of 17.6% which is 2.3-times higher than the 7.5% observed in the matched control population.⁴³ In a prospective cohort study in the Netherlands, 22% of patients with EGPA in sustained remission died over a mean follow-up of 4.3 years (52 ± 25 months), compared to 6% over a mean follow-up of 4.7 years (56 ± 9 months) in a control group matched for age, sex, cardiovascular risk factors, and follow-up duration ($p=0.022$).⁴²

In addition, the UK-specific CPRD data have shown that the mortality risk varies dependent on the EGPA health state. Patients in relapse have the greatest mortality risk, with a standardised mortality ratio (SMR) of ■■■ when compared to the general population in England.² Conversely, patients with the lowest mortality risk are those in remission, who experience a SMR of ■■■.² In support of the CPRD data, in a physician survey study covering 243 patients with EGPA, the reported 10-year mortality rate was 40% in patients with relapsed or refractory disease compared with 10% in the general EGPA cohort.⁴⁴

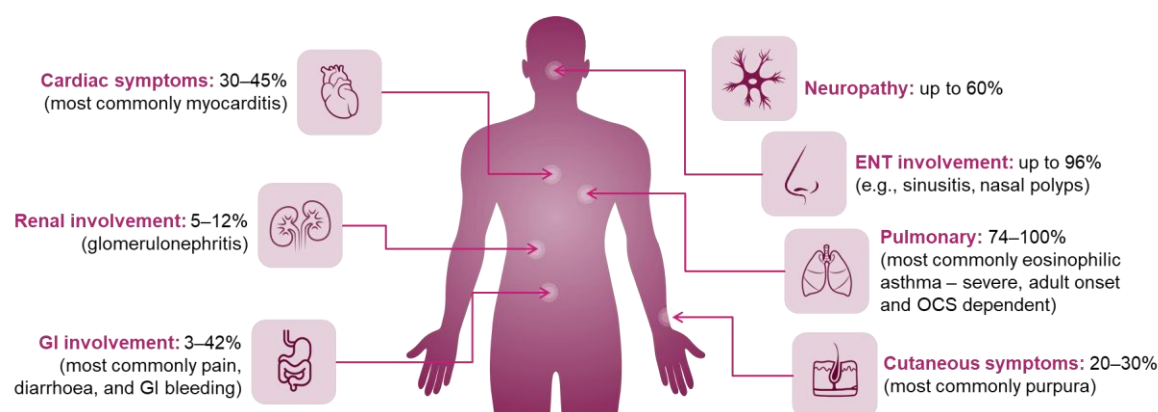
B.1.3.2 Disease burden

Symptom burden

EGPA causes a range of disease manifestations across multiple organ systems, causing organ damage and creating significant long-term health consequences for patients.

Patients with EGPA may first experience severe, adult-onset asthma, a high frequency of ENT symptoms, fatigue, pain, weight loss and fever. Following this, elevated levels of eosinophils infiltrate organ systems, particularly the lungs, heart, and GI system. Eosinophils also cause the inflammation of small and medium blood vessels which results in progressive organ damage.⁴⁵ It has been found that persistent damage to at least one organ at diagnosis was observed in 28.6% of patients in a retrospective Clinical Practice Research Datalink (CPRD) analysis of 283 patients with EGPA, emphasising the long-term effects of the disease.^{2, 46} Considering the multi-system impact of EGPA, patients experience a broad range of immediate manifestations including chronic asthma, peripheral neuropathy and chronic sinusitis which contribute to the significant clinical and patient burden in EGPA. Overall, commonly reported symptoms are outlined in Figure 3 and below.

Figure 3: The organ systems impacted by EGPA



Abbreviations: ENT: ear-nose-throat; GI: gastrointestinal; OCS: oral corticosteroid

Source: Adapted from Trivoli G, *et al.* Rheumatology 2020;⁴⁵ Cottin V, *et al.* European Respiratory Journal;⁴⁰ Doubelt I, *et al.* ACR Open Rheumatology⁴⁷

Eosinophilic infiltration affects multiple organ systems, causing a range of severe, complex and debilitating manifestations affecting many aspects of daily living:

- The majority (74–100%) of patients with EGPA have **asthma** at diagnosis,^{38, 46, 48-51} with asthma pathology also driven by high levels of eosinophilic inflammation.⁴⁰ Based on literature, an average of 57.9% of patients with EGPA had severe asthma aligned with the definition of Global Initiative for Asthma (GINA) Step 5⁵¹⁻⁵³
- **Cardiac manifestations** such as cardiomyopathy, pericarditis and myocarditis are also common in patients with EGPA.^{11, 18} These cause immediate symptoms of shortness of breath, chest pain and irregular heartbeat, with further disease progression resulting in heart failure, heart attack and thrombosis
- Neurological manifestations predominantly include mononeuritis multiplex, a peripheral **neuropathy** that affects up to 60% of patients with EGPA.^{38, 40, 47, 49, 51, 54-57} In mononeuritis multiplex, damage occurs to multiple, individual peripheral nerves (nerves outside of the central nervous system). This leads to neuropathic pain and sensory and motor deficits, including weakness in limbs, loss of feeling, tingling or paralysis in areas of the body, resulting in difficulties with walking, standing, lifting and carrying objects^{58, 59}
- **GI manifestations** are also common, occurring in 3–42% of patients, and include abdominal pain (20–25%), haemorrhage (3–9%) and colitis (2–3%)^{45, 47, 51, 54, 55, 57, 60, 61}
- **ENT manifestations**, such as rhinitis, sinusitis and nasal polyps (soft growths in the lining of the nasal passage), present in up to 96% of patients with EGPA.^{47, 49, 51, 54-56} Nasal polyps can cause complications due to blocked airflow and fluid drainage, often resulting in sinus infections and symptoms such as nasal congestion, reduced sense of smell or taste and difficulty breathing⁶²
- Similarly, **renal manifestations** can cause permanent kidney damage and potentially kidney failure, resulting in symptoms like tiredness, loss of appetite and nausea. Patients may also require dialysis or transplants, further increasing the disease burden^{63, 64}

Patients with EGPA experience disease manifestations at a higher incidence than those with other chronic diseases. A US MarketScan study of patients with EGPA (n=182) compared with patients with severe, uncontrolled asthma (n=640), demonstrated that patients with EGPA had

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

increased occurrence of cardiac comorbidities (19.8% versus 10.5%; $p<0.001$), including ischaemic heart disease (18.7% versus 12.0%; $p=0.019$), and cardiomyopathy (5.5% versus 1.3%; $p=0.002$) at diagnosis.⁶⁵ Additionally, patients with EGPA also had increased occurrences of respiratory failure (19.2% versus 2.8%; $p<0.001$) and haematuria (the presence of blood in urine; 8.2% versus 2.5%; $p=0.002$).⁶⁵ Post diagnosis, patients with EGPA experienced increased numbers of ENT (55.5% versus 24.7%; $p<0.001$), ocular (22.5% versus 14.4%; $p=0.007$) and renal (6.0% versus 1.9%; $p=0.004$) manifestations.⁶⁵

Impact on patient and carer quality of life

EGPA is characterised by heterogeneous, hypereosinophilic manifestations and organ damage which contribute to a considerable, negative impact on many aspects of quality of life. Patients experience multiple disruptions to daily living including severe fatigue, functional impairment, sleep disruption, emotional distress, anxiety and a reduced ability to work and engage in social activities. This is exacerbated by the frequent relapses and ineffective treatment options. EGPA also affects carers' mental health and ability to work

As noted in Section B.1.3.1, EGPA is a poorly characterised rare disease, resulting in limited available literature detailing the impact of EGPA on HRQoL. As part of the extensive work undertaken by AstraZeneca to deepen the understanding of the disease, a literature review, an advisory board with patients, consultation with clinical experts and a UK-specific vignette study were conducted. The vignette study included consultation with patients with EGPA through eight in-depth interviews and with clinical experts through four in-depth interviews, in line with NICE's guidance on structured elicitation methods (described further in Section B.3.4.4).^{39, 66}

Collectively, all the gathered insights indicated that the clinical manifestations of EGPA have a considerable, negative impact on patients' HRQoL and daily activities. The heterogeneous, hypereosinophilic manifestations and organ damage associated with EGPA lead to a reduced ability to exercise (74%), impaired sleep quality and quantity (71%), decreased ability to work (63%), limited engagement in social activities (60%) and difficulty walking (54%).^{19, 67} People also report difficulty breathing, substantial fatigue, functional impairment and neuropathy.³⁹ Symptoms such as coughing, wheezing and breathlessness can disrupt sleep, exacerbating existing fatigue, and can have "devastating consequences" due to the impact on "every aspect of people's lives including employment, education, social life, and relationships".³¹ ENT manifestations and the resulting symptoms can lead to sleep impairment, anxiety and depression, while neurological manifestations impact the functional ability of patients, limiting their ability to carry out daily activities.⁶² Collectively, EGPA symptoms also limit patients' ability to engage in usual social interactions, leading to absenteeism and isolation.

In an illness perception questionnaire (IPQ) designed to evaluate an individual's beliefs and perceptions about their condition, patients with EGPA scored 10.5 out of a possible 22 symptoms in the IPQ identity dimension, representing strongly held beliefs about the number of symptoms attributed to the illness.⁶⁸ They also scored 4.3 and 3.9 out of 5.0, for timeline-acute/chronic and consequences dimensions, respectively. These scores indicate strong beliefs that the disease will last over a prolonged period of time and has negatively impacted the respondents' ability to function.⁶⁸

The substantial fatigue experienced by patients with EGPA reduces their ability to remain employed and engage in typical daily activities.⁶⁹ In a questionnaire study of patients with EGPA, the multi-dimension fatigue inventory score, was 16.1 (range 4-20). This is substantially greater

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

than the threshold for defining significant fatigue (≥ 13).⁶⁸ Additionally, patient insights gathered to support this submission further substantiated the significant impact the disease has on daily activities;⁷⁰ patients mentioned “I experienced fatigue and EGPA impacted my ability to exercise”, “Showering on a daily basis was exhausting”, “I couldn’t walk upstairs”.

The literature review and vignette study also revealed that patients with EGPA experience poor mental health feeling low, scared, anxious and frustrated with their condition;³⁹. Once diagnosed, patients may have a negative perception of their future.²⁰ The continuous cycles of remission and relapse, along with ongoing follow ups, contribute to a negative perception of the illness and can induce stress and anxiety as patients struggle to envision a disease-free future.^{22, 24} Patients have expressed living in fear of potential relapse and worsening symptoms.⁷⁰ The impact of EGPA on mental health was prominent across the patient insights gathered where patients made statements such as “It is an anxiety-inducing condition”, “I was in a bad mental health space”, “I feel detached from others”.⁷⁰

As described above, the HRQoL of patients is dependent on EGPA health state (remission, non-refractory, refractory and relapse) as each state is characterised by differing levels of symptom control and, therefore, wellbeing. Worsening symptoms and loss of disease control during relapses, irreversible organ damage and toxicity from the increased OCS/IS doses limit patients’ HRQoL and ability to conduct daily activities.^{3, 21, 26-28} This will result in patients feeling more low, scared and anxious. Results from a study using the 22-item Sino-Nasal Outcome Test (SNOT-22) also demonstrated significantly elevated scores in patients with active EGPA disease versus those in remission, and an increase in scores was associated with subsequent relapse.⁷¹ Patients with refractory disease experience a greater negative impact on mental health than those in relapse; in addition to the impact of severe symptoms on HRQoL and daily living, they feel hopeless and frustrated,³⁹ as their disease has not achieved remission for a prolonged period of time. On the other hand, patients with non-refractory disease will have milder symptoms and, therefore, improved HRQoL compared to those in refractory and relapse states.³ Patients in remission experience mild or no symptoms and therefore, better HRQoL.

There is an indirect burden on carers who are responsible for patients with EGPA. EGPA impacts carers’ ability to remain employed as patients’ disease becomes progressively worse, with many carers experiencing difficulties with taking time off from work.^{25, 72} Moreover, carers help patients cope mentally as they navigate their EGPA journey, from pre- to post-diagnosis, whilst also having to cope with the uncertainty of what is happening themselves. This can heavily impact carers’ mental health, as they face significant fear and the need for constant vigilance when caring for patients with EGPA, resulting in the requirement for support in their own right from healthcare professionals, particularly with the psychological impact of the disease.²⁵ In a qualitative study, 18 patients with ANCA-associated vasculitis (AAV) and their informal carers participated in semi-structured interviews to explore patient experiences and the effects of caring. Of the 18 patients interviewed, 4 had EGPA. During these interviews, a carer for an EGPA patient expressed their worry that “one day we’ll go to bed and I’ll wake up and she won’t. It could be tomorrow.”²⁵

Economic burden

EGPA is associated with a substantial economic burden, due to both NHS healthcare resource use and the reduced work opportunities for patients with the disease

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

EGPA is associated with high healthcare resource use (HCRU) and per-patient costs. A study of HCRU of patients with EGPA in England reported substantial HCRU in the first 12 months following an EGPA diagnosis:¹⁵

- 97.1% of patients have had a GP visit, with a mean number of 16 visits per patient per year
- Patients also required nurse and allied health professionals visits
- The heterogeneous manifestations of EGPA resulted in 33.7%, 31.8% and 25.2% of patients requiring visits to a respiratory, rheumatology and ENT specialists, respectively, adding pressure to NHS resources

Additionally, up to 90.9% of patients have had an inpatient hospital stay, with a median length of stay of 5–11 days per visit.⁷³ A similar proportion of patients required outpatient hospital visits (up to 97.5%) and 77.6% of EGPA patients had an A&E visit.⁷³ The annual HCRU per patient was £14,261.10, highlighting the significant economic burden of EGPA to the NHS.^{15, 73}

The HCRU and per-patients costs are increased in those who experience disease relapse. Those require more frequent hospitalisation and thus incur greater costs compared with those in remission.²

A work productivity and activity impairment (WPAI) questionnaire was conducted in patients with EGPA (US, UK, Germany, Italy, France and Spain) on the Adelphi Disease Specific Programme (DSP) dataset, with data analysed by AstraZeneca.⁷⁴ Overall, 32.1% of 177 patients reported that EGPA impacted their daily activities whilst 20.8% of 82 patients reported overall work impairment (a combination of lost work hours and lost productivity when able to work).⁷⁴ This impact on the working ability of patients with EGPA could result in loss of earnings, creating a financial burden for individuals. Patients also experience economic impacts, such as the expense to travel to healthcare facilities and the loss of time. Furthermore, a questionnaire study of 41 French patients with EGPA reported that 29.3% of patients received disability living allowance, disability pension or had disabled worker status.⁷⁵

B.1.3.3 Clinical care pathway

There are currently no reimbursed treatments for EGPA in the UK, with SoC consisting of high-dose OCS and IS.

The British Society for Rheumatology (BSR) published guidelines in 2014 for the management of adults with ANCA-associated vasculitis (AAV); EGPA is a type of AAV.³⁰ However, over the past decade since 2014, there have been no further advancements in terms of guidelines specifically for EGPA in the UK. Therefore, guidelines from other countries were reviewed, including the European evidenced-based guidelines and those by the American College of Rheumatology (ACR), European Alliance of Associations for Rheumatology (EULAR) and the EGPA consensus task force.^{21, 26-28} Importantly, those guidelines recommend mepolizumab, which is not available for use in EGPA in the UK. Nonetheless, those guidelines could serve as a basis for developing UK-specific recommendations since benralizumab would be expected to follow the same positioning in the treatment pathway as mepolizumab.

Current treatment pathway

The goal of EGPA management is to control active inflammation and suppress the immune response, in order to induce sustained remission, prevent disease relapse whilst also minimising OCS use (and the related AEs and comorbidities).²⁶ However, in the UK, there are currently no

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

treatments indicated for EGPA that are reimbursed by the NHS. Of note, no submission was made to NICE for mepolizumab (TA845).⁷⁶

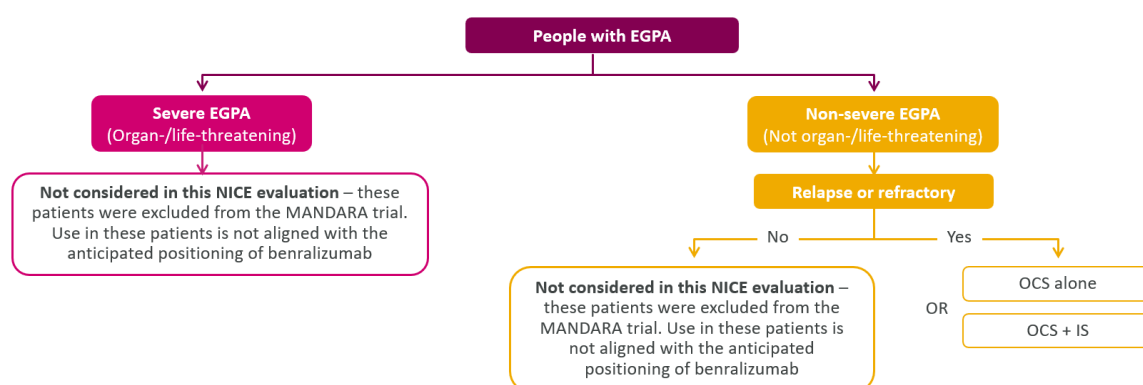
UK clinical expert opinion was elicited and real-world treatment pattern data were collected to characterise the treatment pathway in England.^{3, 4, 21, 26-28} Based on this, standard of care for EGPA consists of sub-optimal, off-label treatments, comprising of high-dose OCS with or without IS.^{21, 26-28}

- OCS are prescribed at high doses, off-label, as the mainstay treatment to induce remission and manage hypereosinophilia by reducing eosinophilic inflammation. Prednisolone is the most commonly prescribed OCS.^{4, 22, 26-28} OCS were prescribed for 86.2% of people with EGPA in a retrospective CPRD study in England over a mean follow-up of 5.4 years post-diagnosis⁴
- Although remission may be achieved in a proportion of patients with high-dose OCS alone, addition of a potent IS therapy is commonly required to induce and/or maintain remission.²⁶⁻²⁸ The CPRD study identified that IS therapies were prescribed for 53.7% of people during the 5.4-year mean follow-up.⁴ The most commonly prescribed IS therapies, according to CPRD analysis include, azathioprine, methotrexate and mycophenolate mofetil.^{3, 4, 27} This was validated by clinical experts as being reflective of UK clinical practice³

As outlined in Section B.1.1, CYC and RTX are not part of UK SoC for the population of interest. These agents are restricted to the treatment of patients with severe EGPA, defined as life- or organ-threatening EGPA,³ and would therefore have a different positioning in the EGPA treatment pathway, compared to the anticipated positioning of benralizumab. UK prescription data analysis confirmed that CYC was restricted to treating severe patients and RTX was only sparingly used in UK clinical practice, and does not form part of UK SoC, as validated by clinical experts.³

The current treatment pathway for EGPA is outlined in Figure 4.

Figure 4: The current EGPA treatment pathway



Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressants; OCS: oral corticosteroids; NICE: National Institute for Health and Care Excellence

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.1.3.4 Unmet need

Current treatment options are limited and sub-optimal. OCS target high levels of eosinophils but are associated with severe AEs and comorbidities. IS suppress the immune system without specifically targeting hypereosinophilia in EGPA and are associated with toxicity. Additionally, these treatments do not adequately control the disease

OCS are prescribed off-label, as the mainstay treatment to induce remission and manage hypereosinophilia in EGPA. The CPRD analysis identified mean daily doses of OCS ranging from 12.4 to 23.1 mg/day over time in the 5 years following EGPA diagnosis.⁴ These high doses of OCS, which are much higher than OCS doses used in severe asthma, are required to deplete the higher levels of eosinophils, which are up to ten times the normal range (Section B.1.3.1).

OCS are effective anti-inflammatory agents, however, there is substantial evidence associating OCS use with acute and chronic AEs, including type 2 diabetes mellitus (T2DM), cardiovascular disease, osteoporosis, pneumonia, cataracts, sleep apnoea and renal impairment, amongst other conditions.³² Many patients with EGPA experience an accumulation of these comorbidities.³¹⁻³³ Patients highlighted that some immediate side effects of OCS treatment included mood swings, weight gain and night sweats, with weight gain affecting self-confidence and mental well-being.⁷⁷

Clinical experts have identified a link between OCS dose and the severity of the side effects which is supported by the literature.^{33, 78} In a study of 138 patients with AAV, a cumulative OCS dose of ≥ 0.9 g was linked to an 80% likelihood of an increase in glucocorticoid toxicity.⁷⁹ Comparatively, the mean cumulative dosage has been reported to be as high as 6.3 g in patients with EGPA across a mean follow-up duration of 21.7 months,⁸⁰ suggesting the majority of patients are likely to experience OCS-related AEs. Considering the high exposure to OCS in EGPA, clinicians highlighted the urgent need to minimise OCS reliance, and consequently the important benefit associated with even tapering or stabilising the OCS dose (as observed in the non-refractory state).³

Additionally, IS are used in EGPA management, however, they do not directly target eosinophils, instead suppressing the immune system. IS treatment is associated with a high risk of organ toxicity and side effects including cytopenia, hepatotoxicity, and major infections such as bacterial pneumonias herpes zoster recurrences, opportunistic infections and *Pneumocystis jiroveci* pneumonia.^{21, 26-28} The side effects of both OCS and IS have a considerable negative impact on quality of life, adding to the physical and mental burden for patients and requiring more frequent healthcare visits.

Patients have also expressed their concern at the current treatment options available and the impacts on their health. Insights gathered from EGPA patients indicated that they “worried about the side effects of their treatments, particularly the steroids”, “the biggest challenge became the drugs and not the condition itself” and “they were keen to get off steroids”.⁷⁰

Furthermore, the combination of OCS and IS is ineffective at maintaining remission, as acknowledged by the British Thoracic Society (BTS).⁸¹ As a result, relapse rates are high and the time to relapse is short. When treated with OCS alone or in combination with IS, 33–67% of patients experience remission, however, up to 82% of patients who achieve remission will relapse, within less than a year.³³⁻³⁵ High relapse rates from OCS and IS have a two-fold implication. Firstly, relapsed disease is treated with increased doses of OCS and IS, which

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

further exacerbates the risk of OCS-related AEs and IS-related toxicity. Secondly, the cycles of relapsing-remitting disease cause patients to feel low, scared, frustrated and anxious, exacerbating negative feelings about future outcomes.

Insights gathered from patients and clinical experts highlighted the acute unmet need for novel therapies that can deplete eosinophils without causing toxicity, to allow a reduction in OCS use, reducing the risk of incidence of acute and chronic OCS-related AEs and IS-related toxicity. Therapies should also induce durable remission, slow disease progression and prevent further organ damage to reduce the burden of disease on patients and the NHS. Therefore, in addition to the natural history of EGPA, the economic analysis for this submission also modelled the impact of OCS use on patients' HRQoL and NHS costs (Section B.3.2.2).

Patients expressed preferences for targeted therapies which would have a greater impact on symptoms compared to SoC, stating that “having something that is new, has a greater positive impact on my condition and is less harmful would be amazing”.⁷⁰

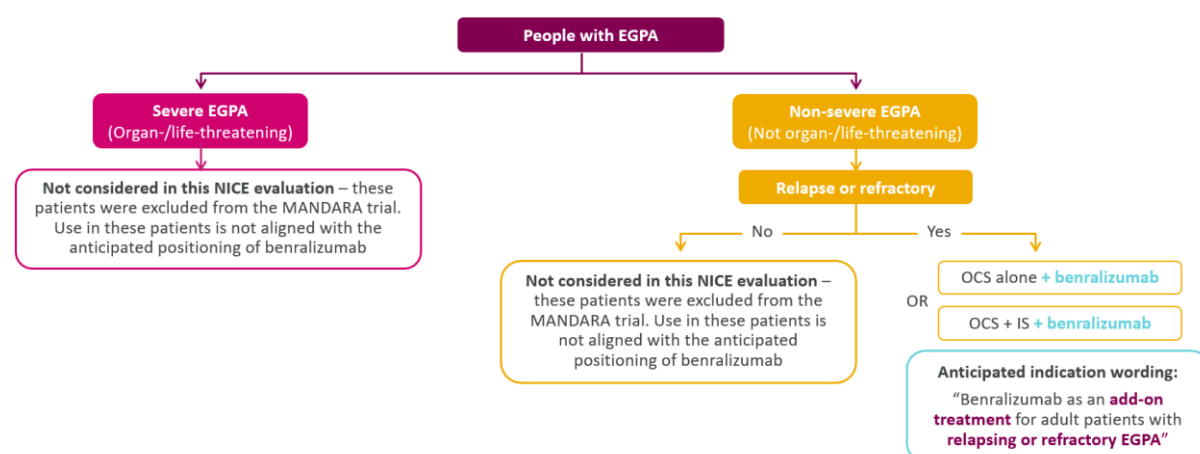
B.1.3.5 Proposed positioning of benralizumab

Benralizumab is an effective treatment option with a favourable safety profile for patients with relapsing or refractory EGPA. Unlike current treatment options, benralizumab has a targeted mechanism of action, rapidly depleting eosinophils, and reducing inflammation (Table 2).

Therefore, benralizumab can address the high unmet need as potentially the first treatment option that effectively induces and maintains remission, enabling to reduce the toxicity and adverse events associated with current SoC.(Section B.2.6).¹

The proposed positioning for benralizumab is as an add-on treatment for adult patients with relapsing or refractory EGPA who are receiving OCS with or without stable IS therapy, as validated by clinical experts.³ (Figure 5).

Figure 5: Potential future clinical care pathway for patients with EGPA



Abbreviations: ACR: American College of Rheumatology; BSR: British Society of Rheumatology; EGPA: Eosinophilic Granulomatosis with Polyangiitis; IS: immunosuppressants; NICE: National Institute for Health and Care Excellence; OCS: oral corticosteroids

Source: BSR guidelines;³⁰ European EGPA guidelines, 2023;²⁶ EULAR guidelines, 2022;²⁸ ACR/Vasculitis Foundation guidelines, 2021;²⁷ EGPA Consensus Task force, 2015²¹

B.1.4 Equality considerations

A consideration was raised during draft scope consultation, regarding comorbid EGPA patients with severe eosinophilic asthma (SEA), already being eligible for treatment with benralizumab. This poses an equality consideration for the following reason:

- Not all patients with EGPA have severe asthma (only 57.9% of patients according to GINA Step 5)⁵¹⁻⁵³
 - Patients with EGPA and comorbid severe asthma would only be able to access benralizumab if they meet the eligibility criteria for its recommendation within severe asthma, i.e. based on blood eosinophil count, prior exacerbation history and being inadequately controlled despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists
 - Even if patients are eligible for benralizumab in severe asthma after meeting these criteria, it is widely understood that access to severe asthma centres in England (where benralizumab is prescribed for severe asthma) is challenging. Despite the inclusion of SA biologics in the NHS England Rapid Uptake Products programme 2021/2022, the biologic uptake rate is still ~20% in this group of patients, based on AstraZeneca's estimates⁸²
 - This inequality was also raised by NHS England in their draft scope response, highlighting the fact that only comorbid patients can access this evidence-based medicine, and only if they have access to a designated severe asthma centre

Furthermore, if patients with EGPA and comorbid severe asthma access benralizumab, the dosing schedule will be in line with SEA dosing (30 mg Q4W for the first 3 doses, then Q8W thereafter), rather than the EGPA dose (30 mg Q4W).

The less frequent asthma dose (30 mg Q8W) has not formally been tested in EGPA, and most real-world data for this dosing frequency are from patients with asthma and EGPA manifestations. A more frequent dose (30 mg Q4W) is considered necessary for EGPA because it is a more severe disease than asthma, and eosinophil levels are often higher.²¹ UK clinicians expressed frustration at the inability to control patients' symptoms at the severe asthma dose and have a strong desire to have access to the dose investigated and proved to be efficacious in MANDARA for EGPA (30 mg Q4W).³

Therefore, AstraZeneca firmly believes that benralizumab needs to be made available for **all** eligible EGPA patients, at the dose that was investigated and proved to be efficacious.

B.2 Clinical effectiveness

The main clinical evidence base for benralizumab as an add-on treatment to SoC in adult patients with relapsing or refractory EGPA was informed from the MANDARA trial

- MANDARA was an international, Phase III, randomised, double-blind (DB), active-controlled, parallel group, multicentre, non-inferiority study comparing the efficacy and safety of benralizumab to mepolizumab, in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy

MANDARA demonstrated the efficacy and safety of benralizumab in adult patients with relapsing or refractory EGPA, receiving OCS with or without IS

- MANDARA met its primary endpoint with benralizumab treatment resulting in remission (BVAS = 0 and OCS dose ≤ 4 mg/day) of EGPA in 40/70 (58%^a) patients showing non-inferiority (NI) to mepolizumab (40/70 [57%^a] patients)¹
- Treatment with benralizumab resulted in durable remission, low annualised relapse rates, reductions in daily dose of OCS, and complete OCS cessation in 40% of patients. Furthermore, treatment with benralizumab improved symptom control, and offered improvements in vasculitis activity, asthma control and pulmonary function⁸³
- [REDACTED]
- The safety profile of benralizumab at the higher dose in EGPA was consistent with the known safety profile of benralizumab in severe asthma

In the absence of head-to-head evidence of benralizumab versus UK SoC, an indirect treatment comparison (ITC) was conducted to generate relative efficacy estimates

- A Bucher ITC, which was anchored through the common comparator arm mepolizumab, compared data from MANDARA and MIRRA to evaluate the comparative efficacy of benralizumab versus SoC^{1, 34}
- Benralizumab showed a statistically significant improvement in the proportion of patients in remission and a reduction in annualised relapse rate, compared with SoC

^a Percentages are expressed as adjusted remission rates, estimated using marginal standardisation methods in a logistical regression model

B.2.1 Identification and selection of relevant studies

A *de novo* clinical systematic literature review (SLR) was conducted in June 2023 and updated in August 2024 to identify relevant clinical evidence on the efficacy and safety of treatments for EGPA published up to August 2024. Full details of the SLR, including the complete methodology and results are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR did not identify any other study beyond the pivotal study for benralizumab in the relevant patient population as defined by the final NICE scope: MANDARA. The pivotal, Phase III MANDARA trial reported evidence on the efficacy and safety of benralizumab as an add-on treatment for adult patients with relapsing or refractory EGPA.¹

An overview of the key clinical evidence from MANDARA is presented in Table 4. The methodology and results of the MANDARA trial are presented from Section B.2.3 onwards.

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 4: Clinical effectiveness evidence

Study	MANDARA (NCT04157348)
Study design	Phase III, international, multicentre, randomised, 52-week DB period, active-controlled, parallel-group, non-inferiority trial with an OLE in which all patients continue treatment with benralizumab
Population	Adult (≥18 years) patients, who have documented EGPA diagnosis based on history or presence of severe asthma, eosinophilia ($>1.0 \times 10^9/\text{litre}$ and/or $>10\%$ of leukocytes) and documentation of at least 2 additional features of EGPA. Patients also had a history of relapsing or refractory EGPA and were on ≥ 7.5 mg daily dose oral corticosteroids, with or without stable immunosuppressive therapy
Intervention(s)	Benralizumab ^a 30 mg Q4W administered as a SC injection
Comparator(s)	Mepolizumab ^a 300 mg (3 x 100 mg) Q4W administered as a SC injection (during the DB period only)
Indicate if trial supports application for marketing authorisation	Yes
Indicate if trial used in the economic model	Yes
Rationale if study not used in the model	N/A
Reported outcomes specified in the decision problem^b	Primary outcome • Remission rate Secondary outcomes • Total accrued duration of remission • Time to first relapse • Number of relapses (relapse rate) • Reduction in OCS use • Use of IS • Annualised relapse rate • Vasculitis activity scores (presented as BVAS scores) • Pulmonary function (ACQ-6 and spirometry) • AEs • HRQoL
All other reported outcomes	• Clinical benefit (defined as one of the following) and complete response (defined as all of the following): ○ Remission (BVAS = 0 and OCS dose ≤ 4 mg/day) at any time during the DB treatment period ○ $\geq 50\%$ reduction in average daily OCS dose during Weeks 48 through 52 ○ EGPA relapse free during the DB treatment period

Footnotes: ^a in addition to OCS with or without IS; ^b endpoints marked in bold are those that are used to inform the cost-effectiveness model.

Abbreviations: AE: adverse events; BVAS: Birmingham Vasculitis Activity Score; DB: double-blind; EGPA: eosinophilic granulomatosis with polyangiitis; HRQoL: Health-Related Quality of Life; mg; milligram; OCS: oral corticosteroids; OLE: open-label extension; Q4W: every 4 weeks; SC: subcutaneous.

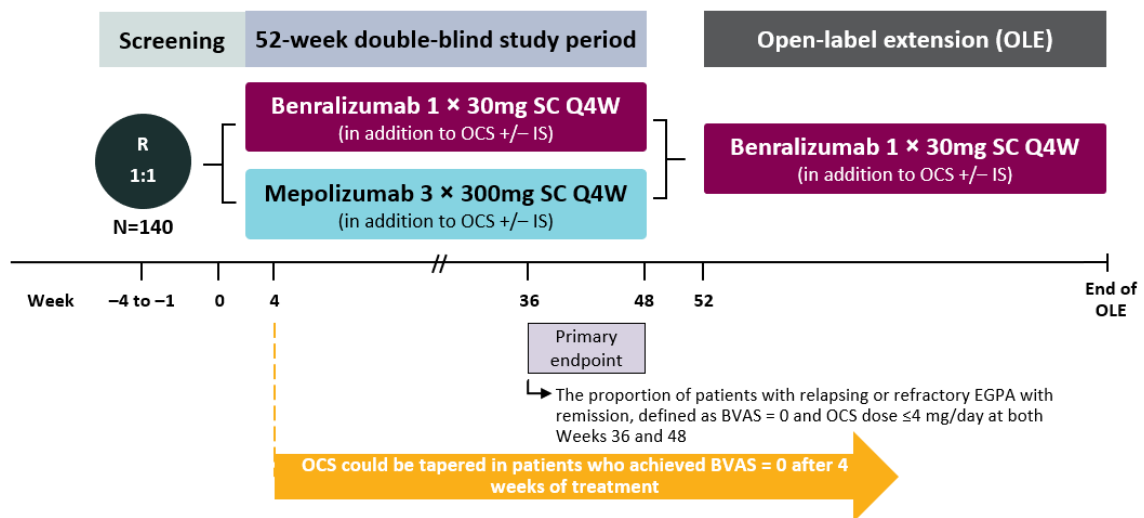
Source: Wechsler M, *et al.* New England Journal of Medicine 2024;¹ AstraZeneca MANDARA CSR, 2023;⁸³ AstraZeneca MANDARA protocol, 2023.⁸⁵

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

B.2.3.1 Summary of trial methodology

A summary of the MANDARA trial methodology is presented in Table 5. MANDARA included a screening period (up to four weeks), a 52-week DB period and an ongoing OLE in which all patients continued treatment with benralizumab, as shown in Figure 6.

Figure 6: MANDARA study design



Footnotes: The primary database lock occurred at Week 52 following completion of the treatment period

Abbreviations: BVAS: Birmingham Vasculitis Score; IS: immunosuppressant; mg: milligram; N: total number of patients; OCS: oral corticosteroids; OLE: open-label extension; Q4W: every 4 weeks; R: randomised; SC: subcutaneous

Source: Adapted from Wechsler M, *et al.* New England Journal of Medicine 2024¹

Table 5: Summary of methodology for the MANDARA trial

	MANDARA (NCT04157348)
Location	50 sites in 9 countries (US [9 sites], Belgium [2], Canada [4], France [8], Germany [5], Israel [6], Italy [7], Japan [5], UK [4])
Trial design	• Phase III, multicentre randomised, DB, active-controlled, parallel-group trial with an OLE (Figure 6) • Following the screening period, patients were randomised to receive benralizumab or mepolizumab • Between baseline and Week 4, patients were required to maintain a stable oral prednisolone/prednisone dose of ≥ 7.5 mg/day prednisolone/prednisone (but not >50 mg/day), with upward adjustments permitted for clinical management of the patient • From Week 4 onwards, if the patient's BVAS equalled zero (i.e. least severe score), their oral prednisolone/prednisone dose was to be tapered downwards according to standard practice. If the BVAS was greater than zero, the oral glucocorticoid dose could be tapered downward at the investigator's discretion • The final dose of the DB treatment period was given at Week 48 with the treatment period reaching completion at Week 52, at which point the primary database lock occurred • All patients who completed the 52-week treatment period were eligible to continue into the OLE, where patients, including those receiving mepolizumab during the DB period, were followed for at least one year and treated with open-label benralizumab, at a dose of 30 mg administered subcutaneously Q4W • Appropriate use of the BVAS was supported by the Study Oversight Committee to ensure data quality and reliability
Method of randomisation	140 patients were randomised in a 1:1 ratio, stratified by region (North America, Western Europe, Japan) following the screening period to receive either: • Benralizumab, in a 30 mg dose by subcutaneous injection Q4W OR: • Mepolizumab, in a 3 x 100 mg dose by subcutaneous injection Q4W Randomisation codes were assigned from a randomisation list prepared by a computerised system, strictly sequentially in each stratum as patients became eligible for randomisation
Method of blinding	The following measures were taken during the trial to ensure blinding of study participants and personnel investigators throughout the 52-week DB trial period: • Sponsor staff involved in the study, the patients, and the Investigators involved in the treatment of patients or in their clinical evaluation and monitoring were not aware of the treatment allocation • To preserve blinding given the different injection volumes of each study treatment, patients received four injections per treatment visit: one SC injection of benralizumab 30 mg and three SC injections of placebo to mepolizumab, or three SC injections of mepolizumab 100 mg and one injection of placebo to benralizumab • Placebo to benralizumab solution was visually matched with benralizumab solution. Placebo to mepolizumab solution was visually matched with mepolizumab solution

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	• All packaging and labelling of the IP were done in such way to ensure blinding for all AstraZeneca and investigational site staff • The information in the randomisation list was kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at Sponsor, or any Contract Research Organisation handling data, had access to the randomisation scheme during the conduct of the DB period
Eligibility criteria	Inclusion criteria • Male or female ≥18 years old • Patients who had a documented EGPA diagnosis • Patients who had been diagnosed with EGPA for at least 6 months before screening visit date based on the history or presence of: asthma plus documented eosinophilia ($>1.0 \times 10^9/\text{litre}$ and/or $>10\%$ of leukocytes) plus documentation of at least 2 additional features of EGPA • History of relapsing or refractory disease, defined as follows: ○ Relapsing disease: patients must have a history of at least one confirmed EGPA relapse (i.e., requiring increase in investigator-initiated OCS dose, initiation or increased dose of immunosuppressive therapy or hospitalisation) within the past 2 years which occurred at least 12 weeks prior to screening whilst receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day ○ Relapsing disease (for Japan): patients must have a history of at least one confirmed EGPA relapse (i.e., requiring increase in investigator-initiated OCS dose, initiation of IV prednisolone or equivalent, initiation or increased dose of immunosuppressive therapy or intravenous immunoglobulins or hospitalisation within the past 2 years which occurred at least 12 weeks prior to screening whilst receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day ○ Refractory disease: failure to attain remission within the 6 months prior to screening (BVAS=0 and OCS dose ≤ 7.5 mg/day prednisolone or equivalent) following induction treatment with a standard regimen, administered for at least 3 months • Patients on a stable OCS dose ≥ 7.5 mg/day prednisolone/prednisone (but not >50 mg/day) for at least four weeks prior to baseline (Visit 2). Maintaining a stable dose of IS and OCS was necessary for accurately assessing the efficacy of benralizumab or mepolizumab and reducing the effects of confounding. If dose adjustment was necessary during the screening period, or the Investigator determined that the patient had not maintained a stable dose, the patient had failed the screen • If receiving immunosuppressive therapy (excluding CYC), the dosage must have been stable for 4 weeks prior to baseline (Visit 2) Exclusion criteria • Diagnosed with granulomatosis with polyangiitis or microscopic polyangiitis

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	• Organ-threatening EGPA: organ-threatening EGPA as per the European League against Rheumatism criteria⁸⁶ ○ i.e., organ failure due to active vasculitis, creatinine >5.8 mg/dL (>513 µmol/L) within 3 months prior to screening (Visit 1) and through randomisation (Visit 2) ○ These patients were excluded to minimise the effects of comorbidities and concomitant medication on the observed efficacy and tolerability of benralizumab or mepolizumab in MANDARA • Imminently life-threatening EGPA disease • Any prior or current treatment with mepolizumab, reslizumab, dupilumab, or benralizumab was prohibited, either as a marketed or investigational biologic; IM, IV, or SC corticosteroids in the 4-week period prior to baseline; oral CYC within 2 weeks prior to baseline and IV CYC within 3 weeks prior to baseline; or rituximab within 6 months prior to baseline A full list of eligibility criteria is available in the MANDARA protocol, 2023⁸⁵
Permitted and disallowed concomitant medication	Allowed concomitant therapies: • Inhaled and topical steroids Restricted concomitant therapies (allowed with limitations on usage): • Inactive/killed vaccinations • Allergen immunotherapy • IS therapy • OCS therapy • Live attenuated vaccines • Blood products • Marketed biologic products Prohibited concomitant therapies (not permitted and patients must adhere to defined washout periods before screening): • Mepolizumab, benralizumab, dupilumab and reslizumab • Omalizumab • Rituximab • IV or SC immunoglobulin • Interferon-α • Anti-tumour necrosis factor therapy • Anti-CD52 (alemtuzumab)

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	• IV, IM or SC corticosteroid therapy • CYC • Other investigational agents (biologic or non-biologic) • Acetaminophen For full information on concomitant therapy, see AstraZeneca MANDARA CSR, 2023⁸³
Primary outcomes	• The proportion of patients with relapsing or refractory EGPA with remission, defined as BVAS = 0 and OCS dose $\leq$4 mg/day (main remission definition) at both Weeks 36 and 48^{34, 87} • Supportive endpoint: Proportion of patients with remission defined by BVAS = 0 and OCS dose $\leq$7.5 mg/day (supportive remission definition) at both Weeks 36 and 48⁸⁶
Secondary outcomes	• Accrued duration of remission ◦ The duration of clinical remission (defined as accrued duration in weeks) was collected for the following categories: 0 Week, >0 to <12 Week, 12 to <24 Week, 24 to <36 Week, $\geq$36 Week with analysis repeated based on main and supportive remission definitions • Time from randomisation to first EGPA relapse ◦ Relapse was defined as any of the following: active vasculitis (BVAS > 0); active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting any of the following: an increased dose of OCS therapy to >4 mg/day prednisolone total daily dose; an increased dose or addition of immunosuppressive therapy; hospitalisation related to EGPA worsening • Use of OCS dose during Weeks 48 to 52 ◦ The average daily dose of OCS from Week 48 through Week 52 ◦ The proportion of patients with an OCS reduction from baseline • Clinical benefit and complete response (as defined in Table 4) • ARR • Maintenance of remission ◦ The proportion of patients with remission within the first 24 weeks and who remained in remission for the remainder of the DB treatment period. Analysis was repeated based on main and supportive remission definitions • PROs ◦ BVAS, VDI, pulmonary function testing, asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT 22 questionnaire), health-related quality of life (SF-36v2), PGIS, WPAI-GH and blood eosinophil counts assessed as change from Baseline over the 52-week DB treatment period ◦ PGIC assessed as response proportions at each weekly assessment between Visits 2 and 4

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Exploratory outcomes	• To assess the cumulative OCS use in response to treatment with benralizumab compared to mepolizumab • To evaluate the effect of benralizumab compared to mepolizumab on healthcare resource utilisation due to EGPA • To evaluate the effect of benralizumab compared to mepolizumab on biomarkers of inflammation • To evaluate the effect of benralizumab compared to mepolizumab on biomarkers related to the MoA, eosinophilic inflammation, and EGPA disease pathogenesis, as well as baseline predictors of response to benralizumab or mepolizumab • To characterise the patient-reported experience and treatment benefits of benralizumab compared with mepolizumab through patient interviews
Pre-specified subgroup analyses	The pre-specified subgroup analyses were: • Blood eosinophil count (<150 cells/μL or ≥150 cells/μL) • Body mass index (≤30 kg/m² or >30 kg/m²) • OCS use at baseline (<12 mg/day or ≥12 mg/day) • Gender (Male or Female) • Age group (≥18 to ≤65 years or >65 years) • Geographic region (North America, Japan or Rest of World) • Time since EGPA diagnosis (≤4 years or >4 years) • IS therapy usage at baseline (Yes or No) • Baseline VDI score (<5 or ≥5) • Race (White, Asian or Other) • Anti-neutrophil cytoplasmic antibody (ANCA-positive status; Yes or No)

Abbreviations: ACQ-6: Asthma control questionnaire; ANCA: Anti-neutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; CYC; Cyclophosphamide; EGPA: Eosinophilic granulomatosis with polyangiitis; IM: Intramuscular; IP: Investigational product; IV: Intravenous; MoA: mechanism of action; mg: milligram; OCS: Oral corticosteroids; OLE: Open-label extension; PGIC: Patients Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO: Patient-Reported Outcomes; Q4W: Every 4 weeks; SC: Subcutaneous; SF-36v2: Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22: Sino-nasal Outcome Test-22; UK: United Kingdom; US: United States; VDI: Vasculitis Damage Index; WPAI-GH: Work Productivity and Activity Impairment Questionnaire (general health version 2.0)

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023;⁸³ AstraZeneca MANDARA protocol, 2023;⁸⁵ Clinical Trials Gov, 2024.⁸⁸

B.2.3.2 Baseline demographic and disease characteristics

A full comparison of baseline characteristics of patients enrolled in the DB treatment phase is shown in Table 6. Key patient characteristics were well balanced across the two treatment arms, with a similar mean age (52.0 and 52.7 years in the benralizumab and mepolizumab treatment arms, respectively) and proportion of patients in each age group (████% and █████% in the ≥18 to ≤65 years group).^{1, 83} Considering the rarity of EGPA and the trial sample size of 140 participants, both the benralizumab and mepolizumab arms had a similar proportion of male patients (35.7% and 44.3% respectively) and were well balanced across all racial groups, with White patients making up the highest proportion in both groups (████% and █████%, respectively).⁸³

The profile of EGPA disease history was also similar between treatment arms, with both arms having similar proportions of patients with relapsing and refractory disease, similar mean time since diagnosis and similar vasculitis scores (BVAS and VDI).¹ Patients also had similar baseline eosinophil counts in the benralizumab and mepolizumab arms (306.0 cells/μL and 384.9 cells/μL, respectively).^{1, 83} In terms of prior medication, a similar proportion of patients were using IS therapy at baseline in the benralizumab and mepolizumab arms (37.1% and 34.3%) and had a similar mean OCS dose (11.1 mg/day and 11.0 mg/day, respectively).¹ The mean BMI was also similar across both benralizumab and mepolizumab arms (████ kg/m² and █████ kg/m², respectively).^{1, 83} BMI can impact the patients' response to OCS, with a higher BMI associated with poor responses.

As described in Section B.1.3.1, EGPA can occur at any age but is rare in children, with a median age of diagnosis of 57.4 years and it affects males and females equally.¹⁵ Whilst the study population recruited slightly more females than males, there were no known differences related to age, race, ethnic group or geography. Overall, patient demographics from MANDARA were deemed representative of patients with EGPA in the UK, as validated by clinical experts.³

Table 6: Baseline patient and disease characteristics in the MANDARA trial

Characteristic	Benralizumab (N=70)	Mepolizumab (N=70)
Age, years		
Mean (SD)	52.0 (13.9)	52.7 (14.4)
Median (min, max)	55.0 (20, 76)	55.0 (19, 79)
≥18 to ≤ 65 years, n (%)	████	████
>65 years, n (%)	████	████
Sex, n (%)		
Male	25 (35.7)	31 (44.3)
Female	45 (64.3)	39 (55.7)
Race, n (%)		
White	████	████
Asian	████	████
Other	████	████
Missing ^{a, b}	████	████
Region, n (%)		
North America	16 (22.9)	16 (22.9)
Japan	4 (5.7)	4 (5.7)
Rest of World	50 (71.4)	50 (71.4)

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

BMI, kg/m²		
Mean (SD)	██████	██████
Median (min, max)	██████	██████
EGPA disease type, n (%)		
Relapsing disease	45 (64.3)	48 (68.6)
Refractory disease	42 (60.0)	42 (60.0)
Relapsing and refractory disease	18 (25.7)	20 (28.6)
Eosinophil count,^c cells/μL		
Mean (SD)	306.0 (225.0)	384.9 (563.6)
Median (min, max)	240.0 (30, 920)	225.0 (0, 3830)
≥150, n (%)	██████	██████
BVAS^d		
Mean (SD), mg/day	2.3 (3.5)	1.9 (2.9)
Median (mix, max)	██████	██████
>0, n (%)	34 (48.6)	33 (47.1)
Historical ANCA-positive, n (%)	██████	██████
OCS use^e		
Mean (SD), mg/day	11.1 (4.6)	11.0 (5.9)
Median (mix, max)	10.0 (5.0, 30.0)	10.0 (7.5, 40.0)
≥12 mg/day, n (%)	18 (25.7)	14 (20.0)
Immunosuppressive therapy use at baseline, n (%)	26 (37.1)	24 (34.3)
VDI score^f		
Mean (SD)	4.0 (1.8)	4.0 (1.8)
Median (min, max)	██████	██████
≥5, n (%)	23 (32.9)	21 (30.0)
Time since diagnosis of EGPA, years		
Mean (SD)	5.4 (5.4)	4.9 (5.9)
Median (min, max)	████ (0.6, 24.0)	████ (0.1, 38.0)
>4, n (%)	██████	██████

Footnotes: ^a Patients with missing race are from French sites due to local regulation

^b Percentage vales are calculated, not reported

^c Patients entered MANDARA on stable OCS with or without IS, as per the inclusion criteria, and therefore, their eosinophils were being suppressed. As a result, the baseline eosinophil counts for patients in MANDARA were lower than would be expected for patients with EGPA who are not receiving treatment

^d The BVAS ranges from 0 to 59, with higher scores indicating more severe disease

^e The dose of oral glucocorticoid was calculated as the daily dose of prednisone or prednisolone, regardless of the reason for administration

^f Scores on the VDI range from 0 to 64, with higher scores indicating greater organ damage

Abbreviations: ANCA: anti-neutrophil cytoplasmic antibodies; BMI: body mass index; BVAS: Birmingham Vasculitis Activity Score; EGPA: Eosinophilic granulomatosis with polyangiitis; max: maximum; mg: milligram; min: minimum; N: number of patients in treatment group; OCS: oral corticosteroids; SD: standard deviation; VDI: Vasculitis Damage Index

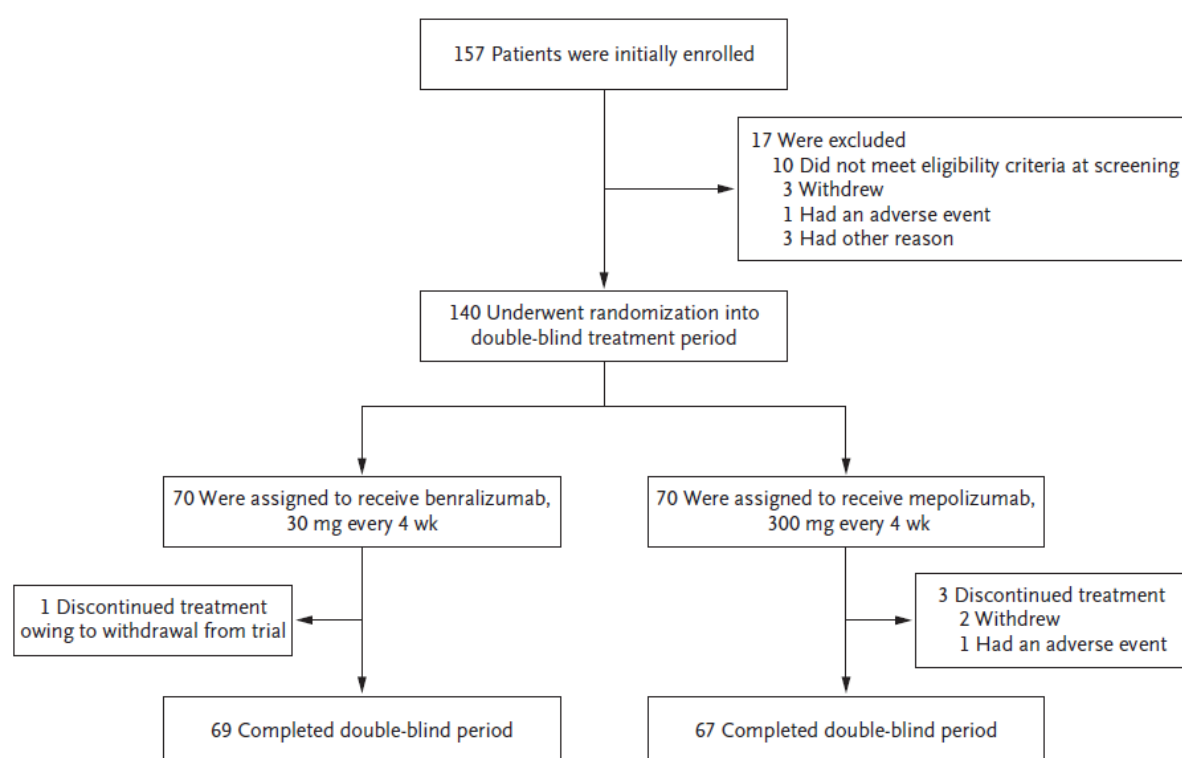
Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

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

B.2.4.1 Trial populations in MANDARA

As summarised in Figure 7, 140 patients were randomised in a 1:1 ratio in MANDARA to receive either benralizumab or mepolizumab. The definitions of the MANDARA trial populations considered in this submission are presented in Table 7. The population used in the analysis of the primary and secondary efficacy endpoints was the full analysis set population, whilst safety analyses used the safety analysis set.

Figure 7: Patient enrolment and randomisation in MANDARA



Abbreviations: mg: milligram; wk: week

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024¹

Table 7: Description of populations for analyses

Population	Description
Full analysis set (N=140)	All patients who were randomised and received at least one dose of IP are included, irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised treatment irrespective of whether they prematurely discontinued according to the ITT principle. Patients who withdrew consent to participate in the study were included up to the date of their study termination. All efficacy analyses were analysed using the full analysis set
Safety analysis set (N=140)	The safety analysis set consisted of all patients who received at least one dose of IP. A patient who received

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	active IP (benralizumab) on one or several occasions was classified as active (benralizumab)

Abbreviations: IP: investigational product; ITT: Intent to Treat; N: number of patients in each population

Source: AstraZeneca MANDARA protocol, 2023⁸⁵

B.2.4.2 Statistical analysis

Primary analysis

The primary objective of the MANDARA trial was to assess the durability of response to treatment with benralizumab compared with mepolizumab in patients with relapsing or refractory EGPA who were receiving SoC therapy, assessed by the proportion of patients in remission at both Weeks 36 and 48 (EGPA remission was defined as BVAS = 0 and OCS $\leq$ 4 mg/day).⁸³ The primary analysis demonstrated the non-inferiority (NI) of benralizumab versus mepolizumab based on the primary endpoint of remission and the primary analysis data cut-off was the 10th of August 2023. Details of the statistical analysis for the primary efficacy endpoint are presented in Table 8, while details of statistical analysis for secondary endpoints can be found in the MANDARA protocol.⁸⁵

Table 8: Statistical methods for the primary analysis in MANDARA

Hypothesis objective	- The null hypothesis for the primary efficacy analysis was that the proportion of patients achieving remission on benralizumab was inferior to that of patients on mepolizumab by a NI margin of –25% - The alternative hypothesis was that benralizumab was non-inferior to mepolizumab - The primary endpoint was considered to have been met if benralizumab demonstrated non-inferiority to mepolizumab
Statistical analysis	- The primary endpoint was evaluated using the marginal standardisation method in logistic regression, with adjustment for treatment group, baseline, OCS dose, baseline BVAS and region (North America, Japan or the rest of the world) - From this model, the absolute difference in the percentage of patients with remission (benralizumab minus mepolizumab) was estimated, along with the associated two-sided 95% CI - To show non-inferiority, the lower 95% CI for the absolute difference between benralizumab and mepolizumab needed to be above the prespecified margin of –25 percentage points. - If the primary analysis showed non-inferiority, a formal test for the superiority of benralizumab to mepolizumab at the two-sided 0.05 level (equivalent to a one-sided 0.025 level with a treatment effect favouring benralizumab) was conducted with the use of the same model
Sample size, power calculation	The sample size was determined from the assumption that benralizumab and mepolizumab each have a remission rate of 32%. Therefore, 140 patients would provide approximately 90% power to demonstrate NI with a NI margin of –25% at the 2.5% one-sided significance level
Data management, patient withdrawals	- To ensure correct data management, all patient data relating to the study was recorded on printed or eCRF unless transmitted to AstraZeneca or the designee electronically - The Investigator was responsible for verifying data entries and permitting study-related monitoring, audits, IRB/IEC review and regulatory agency inspections and providing direct access to source

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	data document • Study monitors performed ongoing source data verification to confirm that data entered into the eCRF was accurate, complete and verifiable and that the study was conducted in accordance with the currently approved protocol, other study agreements, ICH GCP and all applicable regulatory requirements • Records and documents including signed ICFs must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulation, according to the AstraZeneca GRAD schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca • Patients could withdraw from the study at any time, at their own request and without prejudice to further treatment • If a patient withdraws consent, it is the Investigator's responsibility to evaluate the patient and to ensure the patient receives appropriate treatment according to their clinical status/condition. A withdrawal visit will be conducted to collect as much data as possible. If a patient withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before withdrawal of consent. If a patient only withdraws consent for the retention of biological samples, the patient is not withdrawn from the study

Abbreviations: eCRF: electronic case report form; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; GRAD: Global Retention and Disposal Schedule; ICF: informed consent form; IEC: Independent Ethics Committee; ICH GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; IRB/IEC: Institutional Review Board/Independent Ethics Committee; OCS: oral corticosteroids

Source: AstraZeneca MANDARA protocol, 2023⁸⁵

NB: This testing strategy for the primary endpoint required no multiplicity adjustment as it corresponded to a simple closed test procedure and involved only one dose level of the test treatment, benralizumab, relative to mepolizumab. There was no multiplicity protection for secondary or exploratory endpoints or subgroup analyses, and therefore, the results of these analyses are reported as point estimates and 95% confidence intervals, with all p values being nominal.¹ Furthermore, the widths of the of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary end points.¹

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A critical appraisal of the identified clinical effectiveness evidence was carried out and is summarised in Table 9

Table 9: Critical appraisal of clinical effectiveness evidence

Was randomisation carried out appropriately?	Yes. All patients were centrally assigned to randomised study treatment using an interactive voice response system or interactive web response system
Was the concealment of treatment allocation adequate	Yes. The placebo to benralizumab solution was visually matched with the benralizumab solution. The placebo to mepolizumab solution was visually matched with mepolizumab solution. All packaging and labelling of the IP was done in such way as to ensure blinding for all AstraZeneca and investigational site staff. The placebo to mepolizumab (0.9% sodium chloride) was prepared and dispensed by the study site using labels provided by the unblinded site pharmacist. In order to mitigate potential unblinding on the basis of blood eosinophil counts, per protocol haematology was run by the

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	central laboratory. All patients received 3 vaccines to avoid unblinding by differing vaccine numbers between benralizumab and mepolizumab
Were the groups similar at the outset of the study in terms of prognostic factors	Yes. Potentially eligible patients entered a screening period of up to 4 weeks (minimum of one week) and were required to be on a stable dose of OCS of ≥ 7.5 mg/day prednisolone/prednisone (but not >50 mg/day), for at least 4 weeks prior to baseline (Visit 2). If dose adjustment was necessary during the screening period, or the Investigator determined that the patient had not maintained a stable dose, the patient failed the screen. The demographic and clinical characteristics of the patients at baseline were balanced between the treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The first 52 weeks of this study was a double-blind design: AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of patients or in their clinical evaluation and monitoring of the patients were not aware of the treatment allocation. The information in the randomisation list was kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at AstraZeneca, or any Contract Research Organization handling data, had access to the randomisation scheme during the conduct of the study
Were there any unexpected imbalances in drop-outs between groups?	No. There were no unexpected imbalances in the drop-outs between the benralizumab arm and the mepolizumab arm. There was one discontinuation in the benralizumab arm due to patient withdrawal. There were three discontinuations in the mepolizumab arm (two due to patient withdrawal and one due to AEs)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Results for all outcomes described in the trial methodology were presented
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The study used an intention-to treat analysis

Abbreviations: AE: adverse event; IP: investigational product; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine 2024¹

B.2.6 Clinical effectiveness results of the relevant trials

The main clinical evidence base for the efficacy and safety of benralizumab as an add-on treatment to SoC in adult patients with relapsing or refractory EGPA was informed from the MANDARA trial. The following sections present the efficacy results for the primary and secondary endpoints of the MANDARA trial. Further results from the MANDARA trial, including interim data from the OLE period, are presented in Appendix N.

B.2.6.1 Primary outcome

Remission rate at Weeks 36 and 48

For the primary endpoint, benralizumab as an add-on treatment (henceforth referred to as “benralizumab”) resulted in main remission (BVAS = 0 and OCS ≤4 mg/day) in 57.7% of patients at both Weeks 36 and 48, compared with 56.5% with mepolizumab (as an add-on treatment), giving a treatment difference of 1.2% (95% CI: -14.1, 16.5; p=0.8773; Table 10).^a

Table 10: Proportion of patients with remission at both Weeks 36 and 48 across both treatment arms (full analysis set)

Remission definition	Treatment group	Number (%) of patients in remission	Adjusted remission rate (%) ^a	Comparison between groups		
				Difference in remission rates (%) ^a	95% CI ^b	p value ^c
Main remission ^d	Benralizumab 30 mg (N=70)	██████	57.7	1.2	-14.1, 16.5	0.8773
	Mepolizumab 300 mg (N=70)	██████	56.5	-	-	-
OCS dose ≤4 mg/day	Benralizumab 30 mg (N=70)	██████	60.6	2.6	-12.7, 18.0	0.7354
	Mepolizumab 300 mg (N=70)	██████	58.0	-	-	-
BVAS = 0	Benralizumab 30 mg (N=70)	██████	83.0	-1.2	-13.3, 10.9	0.8502
	Mepolizumab 300 mg (N=70)	██████	84.2	-	-	-

Footnotes: ^a The adjusted remission rates and the difference (benralizumab – mepolizumab) were estimated using marginal standardisation method in a logistic regression model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region (North America, Rest of World, and Japan). Baseline was defined as the last measurement on or prior to the date of randomisation.

^b The NI test was assessed using a NI margin of -25%. The lower 95% CI for the absolute difference between benralizumab and mepolizumab remission rates needs to be above the NI margin of -25%.

^c 2-sided superiority p value testing differences between treatment groups (equivalent to a 1-sided 0.025 level).

^d Main remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day (in the event a patient reached remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission). Supportive remission is defined as BVAS = 0 and OCS dose ≤ 7.5 mg/day. Results for the supportive remission endpoint definition are presented in Appendix N.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; N: number of patients in treatment group; NI: non-inferiority; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

NB: The results indicated statistical non-inferiority but not superiority of benralizumab to mepolizumab, since the lower bound of 95% CI exceeded -25 percentage points and the two-sided p-value for superiority was greater than 0.05.¹ Here, the p-value is interpreted in the context of a null hypothesis that benralizumab is inferior to mepolizumab by more than the non-inferiority margin (Section B.2.4.2). Therefore, a p-value greater than 0.05 suggests that there is not enough statistical evidence to conclude that benralizumab is inferior to mepolizumab by more than the pre-specified margin.

B.2.6.2 Secondary outcomes

Remission within the first 24 weeks and remaining in remission for the remainder of the DB period

Similar proportions of patients in the benralizumab group compared with the mepolizumab group achieved remission (BVAS = 0 and OCS $\leq$ 4 mg/day) within the first 24 weeks of treatment and remained in remission through Week 52, (difference of 5.5% in favour of benralizumab [95% CI: -9.3, 20.4; p=██████]). Full results are presented in Table 11.⁸³

Table 11: Proportion of patients with main remission within the first 24 weeks and remaining in remission for the remainder of the DB period until Week 52 (full analysis set)

Remission definition	Treatment group	Number (%) of patients with remission that remained until Week 52	Adjusted remission rate (%) ^a	Comparison between treatment groups		
				Difference in remission rates ^a	95% CI	p value ^c
Main remission ^b	Benralizumab 30 mg (N=70)	██████	42.1	5.5	-9.3, 20.4	██████
	Mepolizumab 300 mg (N=70)	██████	36.5	-	-	-

Footnotes: ^a The remission rates, the difference (benralizumab – mepolizumab) and 95% CI were estimated using marginal standardisation method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS and region.

^b Main remission was defined as BVAS = 0 and OCS dose $\leq$ 4 mg/day (in the event a patient was in remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission). Supportive remission is defined as BVAS = 0 and OCS dose $\leq$ 7.5 mg/day (in the event a patient had was in remission and at any subsequent visit has a BVAS = 1 which did not require an increase in OCS dose above 7.5 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission). Results for the supportive remission endpoint are presented in Appendix N.

^c 2-sided p-value testing differences between treatment groups (equivalent to a 1-sided 0.025 level). p values were not multiplicity adjusted.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; DB: double-blind; N: number of patients in treatment group; OCS: oral corticosteroids

Source: AstraZeneca MANDARA CSR, 2023⁸³

Time to first relapse

Benralizumab was associated with a similar time to first relapse compared with the mepolizumab group (HR: 0.98; 95% CI: 0.53, 1.82; p=████) based on a Cox-proportional hazards model and log-rank test. Full results are presented in Table 12 and Figure 8. Major relapse occurred in zero patients in the benralizumab group and three patients (4.3%) in the mepolizumab group, meaning that a HR was not calculable.^{1, 83}

Table 12: Time to first relapse and time to first major relapse, Cox-proportional hazard model (full analysis set)

		Benralizumab 30 mg (N=70)	Mepolizumab 300 mg (N=70)
Relapse ^c	Number (%) of patients with relapse	21 (30.0)	21 (30.0)
	Time to first relapse (weeks) (95% CI) ^a		
	1 st quartile	████	████
	Median	████	████
	3 rd quartile	████	████
	Percent patient with at least one relapse (95% CI) ^a		
	By Week 16	████	████
	By Week 32	████	████
	By Week 52	████	████
	p value for unstratified log-rank test	████	
	HR (95% CI) ^b	0.98 (0.53, 1.82)	
Major Relapse ^d	Number (%) of patients with relapse	0 (0.0)	3 (4.3)
	Time to first relapse (weeks) (95% CI) ^a		
	1 st quartile	████	████
	Median	████	████
	3 rd quartile	████	████
	Percent patient with at least one relapse (95% CI) ^a		
	By Week 16	████	████
	By Week 32	████	████
	By Week 52	████	████
	p value for unstratified log-rank test	████	
	HR (95% CI) ^b	Not calculable	

Footnotes: ^a Calculated using the Kaplan-Meier technique.

^b The hazard ratio (Benralizumab versus. Mepolizumab) and 95% CI are estimated using a Cox regression model with Efron method to control for ties. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region. A <1 hazard ratio means benralizumab is favoured.

^c Relapse is defined as worsening or persistence of active disease characterised by: active vasculitis (BVAS >0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalisation related to EGPA worsening.

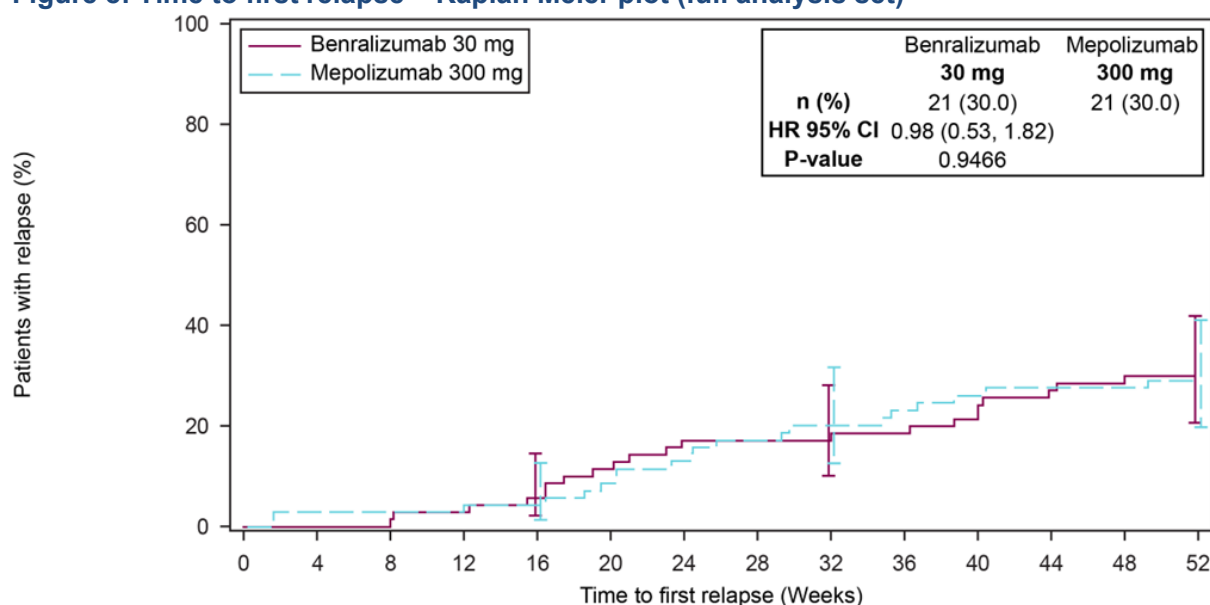
^d Major relapse is a subset of the total relapse events and is defined as any organ or life-threatening EGPA event, BVAS ≥6, an asthma relapse requiring hospitalisation or sino-nasal relapse requiring hospitalisation.

Abbreviations: ACQ-6: Asthma Control Questionnaire (6-item version); BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; EGPA: Eosinophilic Granulomatosis with Polyangiitis; HR: hazard ratio; N: number of patients in treatment group; NE: not estimated; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Figure 8: Time to first relapse – Kaplan Meier plot (full analysis set)



No. of patients at risk													
Benralizumab 30 mg	70	70	70	68	66	62	58	58	58	57	55	51	41
Mepolizumab 300 mg	70	68	68	66	66	63	60	57	54	52	50	49	38

Footnotes: The time to relapse = start date of relapse – date of randomisation + 1 day. If a patient did not experience a relapse by Week 52, their time to relapse was right-censored at the last available assessment time. The relapse was defined as worsening or persistence of active disease characterised by: active vasculitis (BVAS > 0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least 1 of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalisation related to EGPA worsening. One patient had first relapse after Week 52. The lower bound and upper bound of the 95% CI of the estimated proportion of patients with relapse by Week 16, Week 32 and Week 52 are marked on the lines. The OR and its 95% CI were estimated with using a Cox-proportional hazards model with the Efron Method used to control for ties. The covariates in the model included treatment arm, baseline dose of OCS, baseline BVAS and region

Abbreviations: ACQ-6: Asthma Control Questionnaire (6-item version); BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; HR: Hazard ratio; N: number of patients in treatment group; n: number of patients with relapse; OCS: oral corticosteroids; OR: odds ratio

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Annualised relapse rate (ARR)

The ARR was similar in patients treated with benralizumab compared with those treated with mepolizumab. Benralizumab was associated with an estimated ARR of 0.50 (95% CI: [redacted]) with no major relapses, while mepolizumab was associated with an ARR of 0.49 (95% CI: [redacted]), resulting in a rate ratio of 1.03 (95% CI: 0.56, 1.90; p=[redacted]).^{1, 83} There were four major relapses in three patients in the mepolizumab group.¹ Full results are presented in Table 13.

Table 13: Annualised relapse rate and major relapse rate across treatment arms (full analysis set)

Treatment group		Total number of relapses	Total follow-up time (years)	Annualised relapse rate ^a		Comparison between groups ^a		
				Estimate	95% CI	OR	95% CI	p value ^d
Relapse ^b	Benralizumab 30 mg (N=70)	34	■	0.50	■	1.03	0.56, 1.90	■
	Mepolizumab 300 mg (N=70)	30	■	0.49	■	-	-	-
Major relapse ^c	Benralizumab 30 mg (N=70)	0	■	■	■	■	■	■
	Mepolizumab 300 mg (N=70)	4	■	■	■	-	-	-

Footnotes: ^a The estimate of annualised relapse rates, rate ratio (benralizumab/mepolizumab), and the corresponding 95% CIs were calculated using a negative binomial model. The response variable in the model was the number of relapses experienced by a patient up to Week 52. The logarithm of the patient's corresponding follow-up time up to Week 52 was used as an offset variable to adjust for patients having different follow-up times during which the events occur. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS, and region.

^b Relapse was defined as worsening or persistence of active disease characterised by: active vasculitis (BVAS > 0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalisation related to EGPA worsening.

^c Major relapse was a subset of the total relapse events and was defined as any organ or life-threatening EGPA event, BVAS ≥6, an asthma relapse requiring hospitalisation, or sino-nasal relapse requiring hospitalisation

^d p values were not multiplicity adjusted.

Abbreviations: ACQ-6: Asthma Control Questionnaire (6-item version); BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; N: number of patients in treatment group; NC: not calculable; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Average daily dose of OCS

As discussed in Section B.1.3.4, the risk of OCS-related AEs in patients increases with higher OCS doses, with a cumulative glucocorticoid dose of ≥ 0.9 g associated with an increased likelihood of glucocorticoid toxicity in patients with AAV.⁷⁹ Therefore, reducing OCS dose is a key goal in the management of EGPA, as validated by clinical experts.³

Benralizumab was associated with $\geq 50\%$ reduction from baseline in the average daily dose of OCS during Week 48 to 52 in 84.7% patients; this is compared to 73.9% of patients receiving mepolizumab, resulting in a difference of 10.8% (95% CI: -2.3, 23.8; $p=0.1047$).¹ A 100% reduction from baseline in the average daily dose of OCS during Week 48 to 52 was observed in a greater proportion of patients in the benralizumab arm when compared to the mepolizumab arm (41.4% and 25.8%, respectively) resulting in a difference of 15.7% (95% CI: 0.7, 30.7; $p=0.0406$).¹ Additionally, ■■■% of patients in the benralizumab arm received no OCS, compared to ■■■% in the mepolizumab group. Full results are presented in Table 14.

Table 14: Proportion of patients with reduction from baseline in average daily dose of OCS during Weeks 48 through 52 (full analysis set)

	Treatment group	Number (%) of patients with reduction	Adjusted rate (%) ^a	Comparison between groups		
				Difference in rates (%) ^a	95% CI	p value ^b
≥50% OCS reduction	Benralizumab 30 mg (N=70)	59 (84.3)	84.7	10.8	−2.3, 23.8	0.1047
	Mepolizumab 300 mg (N=70)	52 (74.3)	73.9	-	-	-
100% OCS reduction	Benralizumab 30 mg (N=70)	29 (41.4)	41.4	15.7	0.7, 30.7	0.0406
	Mepolizumab 300 mg (N=70)	18 (25.7)	25.8	-	-	-
OCS dose ≤4 mg/day	Benralizumab 30 mg (N=70)	48 (68.6)	68.9	−0.7	−15.6, 14.2	0.9283
	Mepolizumab 300 mg (N=70)	49 (70.0)	69.6	-	-	-
OCS dose =0 mg/day	Benralizumab 30 mg (N=70)	██████	NR	NR	NR	NR
	Mepolizumab 300 mg (N=70)	██████	NR	NR	NR	NR

Footnotes: ^a The rates and the difference (benralizumab – mepolizumab) were estimated using marginal standardisation method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS and region. Baseline was defined as the last measurement on or prior to the date of randomisation.

^b 2-sided p value. p values were not multiplicity adjusted.

If patients withdrew early from the study prior to Week 52, the daily dose of OCS for the last 28 days was used to derive the average daily dose during Week 48 through 52. Patients who withdrew from investigational product before Week 48 were considered non-responders for % reduction in OCS.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; N: number of patients in treatment group; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Blood eosinophil count

As discussed in Section B.1.3.1, EGPA is characterised by increased circulating and tissue eosinophils which cause the inflammation of small or medium-sized blood vessels. Patients with EGPA have very high levels of circulating and tissue eosinophils (up to ten times higher than the normal range).¹⁵

The results of the MANDARA trial indicate that treatment with benralizumab causes the rapid and near-complete depletion of blood eosinophils in patients with EGPA. A reduction in blood eosinophil count from baseline was observed in both treatment groups from Week 1, the first time point assessed, through Week 52, with greater reductions demonstrated in the benralizumab group compared to mepolizumab at all time points. Full results are presented in Table 15.

The rapid and near-complete depletion of blood eosinophils MANDARA participants is expected to have resulted in the observed patient-relevant improvements, such as in lung function (spirometry), vasculitis activity (BVAS), OCS dose reduction and asthma control (ACQ-6).

Table 15: The change from baseline to Week 52 in absolute eosinophil count (full analysis set)

Time point	Statistic	Benralizumab 30 mg (N=70)		Mepolizumab 300 mg (N=70)	
		Absolute eosinophil count (cells/ μ l)	% change from baseline	Absolute eosinophil count (cells/ μ l)	% change from baseline
Baseline ^a	N	70	-	70	-
	Mean (SD)	306.0 (225.0)	-	384.9 (563.6)	-
Week 1	N	■	■	■	■
	Mean (SD)	■	■	■	■
Week 52	N	■	■	■	■
	Mean (SD)	■	■	■	■

Footnotes: ^a Baseline is defined as the last non-missing measurement on or prior to the date of randomisation.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; N: number of patients in treatment group; SD: standard deviation

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Birmingham Vasculitis Activity Score (BVAS)

BVAS is a tool for the assessment of disease activity in systematic vasculitis, which records features that are attributable to vasculitis, after the exclusion of other causes, in different organ-based systems. A scoring sheet is used to record the presence of each item and the total score of nine organ systems gives an indication of the disease activity of each patient and reflects the need for therapy. The higher the score, the more active the vasculitic disease at the time of evaluation, with a maximum possible score of 63 and a score of 0 representing remission.

Benralizumab was associated with an adjusted BVAS response (BVAS score of 0 or 1) at Week 52 in █% of patients, compared with █% of those treated with mepolizumab (Table 16). The difference in response rates was █% (95% CI: █, █; p=█).⁸³

Table 16: BVAS response rate (full analysis set)

	Number (%) of responders	Adjusted response rate ^a (%)	Comparison between groups		
			Difference in response rate	95% CI	p value
Benralizumab 30 mg (N=70)	█	█	█	█	█
Mepolizumab 300 mg (N=70)	█	█	-	-	-

Footnotes: ^a The response rates and the difference (Benralizumab - Mepolizumab) are estimated using marginal standardisation method in a logistic regression model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; N: number of patients in treatment group; SD: standard deviation

Source: AstraZeneca MANDARA CSR, 2023⁸³

Spirometry

Similar changes from baseline in forced expiration volume (FEV₁) and forced vital capacity (FVC) were observed in the benralizumab and mepolizumab groups over the 52-week DB period. The FEV₁ mean change from baseline was █ and █ in the benralizumab and mepolizumab arms, respectively. Furthermore, the mean change in FVC was █ in the benralizumab arm and █ in the mepolizumab arm. This shows modest numerical improvements in FEV₁ and FVC in the benralizumab arm. Full results are presented in Table 17.

Table 17: Spirometry parameters and change from baseline over time (full analysis set)

			Benralizumab 30 mg (N=70)		Mepolizumab 300 mg (N=70)	
Spirometry variable (SI unit)	Time point	Statistic	Result	Change from baseline	Result	Change from baseline
FEV ₁ (L): Pre-BD	Baseline ^a	n	█	-	█	-
		Mean (SD)	█	-	█	-
	Week 52	n	█	█	█	█
		Mean (SD)	█	█	█	█
	Baseline ^a	n	█	-	█	-

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

FVC (L): Pre-BD		Mean (SD)	██████	-	██████	-
	Week 52	n	█	█	█	█
		Mean (SD)	██████	██████	██████	██████

Footnotes: ^a Baseline is defined as the last non-missing measurement on or prior to the date of randomisation.
Abbreviations: BD: Bronchodilator; FEV₁: forced expiration volume in 1 second; FVC forced vital capacity; N: number of patients in treatment group; n: number of patients included in analysis; SI: International System of Units; SD: standard deviation
Source: AstraZeneca MANDARA CSR, 2023⁸³

Additional secondary endpoints

Additional secondary endpoints from the MANDARA trial including the proportion of patients achieving and maintaining remission over specified time points, change from baseline in BVAS, clinical benefit, Vasculitis Damage Index, ACQ-6, and work productivity and impairment are presented in Appendix N. Data for the primary endpoint and relevant secondary endpoints using the supportive definition of remission, rather than the main definition, are also presented in Appendix N.

B.2.7 Subgroup analysis

As per the final scope from NICE for this evaluation, subgroup analyses are not relevant to this submission. However, for completeness, results of prespecified subgroup analyses on the primary endpoint, the proportion of patients who achieved main remission at Weeks 36 and 48, are presented in Appendix E. Results were consistent across subgroups.

B.2.8 Meta-analysis

No meta-analysis was conducted as part of this submission, given that only one trial provided relevant clinical data in line with the decision problem.

B.2.9 Indirect treatment comparison

Context

The MANDARA trial provided a comparison of the efficacy of benralizumab versus mepolizumab, however, mepolizumab is not a relevant comparator for this evaluation as it is not a reimbursed treatment option in the UK. As per the decision problem, the relevant comparator is SoC in UK clinical practice, consisting of OCS with or without IS. Given the lack of head-to-head trial informing the relative efficacy of benralizumab versus SoC in patients with EGPA, an ITC was conducted to generate comparative efficacy estimates.

B.2.9.1 Methods of the indirect treatment comparison

Feasibility assessment

As described in Section B.2.1, an SLR was conducted in June 2023 and updated in August 2024 to identify relevant clinical evidence on the efficacy and safety of treatments for EGPA. The original SLR identified 9 unique clinical studies. Of these 9 studies, 7 were randomised controlled trials (RCTs) and these were included in the feasibility assessment described below. Given RCTs are the gold standard for evaluating the effectiveness of treatments, the 2 non-RCTs were Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

excluded from the feasibility assessment.^{89, 90} The SLR update identified 3 further studies, 2 of which were non-RCTs, so only 1 further study was included in the feasibility assessment.

A feasibility assessment (details in Appendix D) was then conducted with the 8 studies to evaluate data availability, heterogeneity between trials and network connectivity. The MIRRA trial (NCT02020889), which was one of the RCTs identified in the clinical SLR, compared the efficacy of mepolizumab versus SoC (consisting of OCS with or without IS, reflective of UK clinical practice).³⁴ Though multiple studies evaluated SoC (OCS with or without IS), MIRRA was the only trial which allowed for an anchored comparison with the MANDARA trial. The feasibility assessment, therefore, concluded that an anchored ITC between MANDARA and MIRRA would enable comparative efficacy estimates to be generated for benralizumab versus SoC, using mepolizumab as a common comparator arm. Given NICE's preference for anchored ITCs, the other studies were excluded.⁹¹

The MANDARA and MIRRA trials were comparable based on study design.^{1, 34} A list of potential treatment effect-modifiers consisting of eligibility criteria and baseline characteristics reported across both the MANDARA and MIRRA trials were identified. The list also included covariates which have previously been considered treatment effect-modifying following a consultation of the literature.^{34, 92-94} Clinical experts were consulted individually to provide input on what factors should be adjusted for in the comparisons. A pooled rank-ordered list of effect-modifiers was then generated based on the individual rankings from the clinical experts. Though differences in these ranked effect-modifiers were observed between study populations, these differences were not considered by clinicians to be meaningful. The similarity in the trial design, population and outcome measurements was confirmed by clinical experts.³ Therefore, no adjustment for population characteristics was deemed necessary, and a Bucher ITC was considered the most appropriate approach.

A comparison of trial design and patient baseline characteristics across the MANDARA and MIRRA trials is presented in Appendix D.

Bucher ITC methodology

The Bucher ITC has a simple methodology which evaluates the differences between two treatments in two sets of clinical trials and preserves the randomisation of the originally assigned patient groups.

As noted above, SoC in MIRRA, consisted of OCS with or without IS, reflective of UK clinical practice. Therefore, use of data from the SoC arm of MIRRA would produce an indirect comparison of benralizumab versus SoC that is generalisable to UK clinical practice.

The comparative efficacy of benralizumab versus SoC was determined for nine outcomes in total. Two of those were used in the economic analysis and, therefore, further detail is provided on the methodology to generate these 2 outcomes below. Further detail about how these endpoints were defined and the remaining 7 outcomes are presented in Appendix D.

- **Proportion of participants in remission** - For remission (defined as BVAS = 0 and OCS dose ≤ 4 mg/day), a binomial distribution with logit link function (i.e. logistic regression) was performed. An estimate of the odds ratio (OR) and its variance for each intervention versus its comparator was then derived

- **Annualised relapse rate (ARR)** - relapse rates were annualised by applying a log offset of patient-level follow-up. A negative binomial distribution with log link function was used. An estimate of the rate ratio (RR) and its variance for each intervention versus its comparator was derived

Inputs used in the Bucher ITC analysis are outlined below in Table 18.

Table 18: Inputs used in Bucher ITC analysis

Endpoint and type	Trial and comparison	Outcome (OR or RR with 95% CI)
Remission (OR)	MANDARA (benralizumab vs. mepolizumab)	██████████
	MIRRA (SoC vs. mepolizumab)	██████████
Annualised relapse rate (RR)	MANDARA (benralizumab vs. mepolizumab)	██████████
	MIRRA (SoC vs. mepolizumab)	██████████

Abbreviations: CI: confidence interval; OR: odds ratio; RR: rate ratio; SoC: standard of care

To generate the relative efficacy estimates between benralizumab and SoC, the log RR or odds ratio (OR) for treatment effect of SoC versus mepolizumab (informed by the MIRRA trial) was subtracted from the log RR or OR for treatment effect of benralizumab versus mepolizumab (informed by the MANDARA trial). The variance of this value was the sum of the two variances, which was then converted to standard error (SE) by taking the square root. Finally, from the log RR/OR and the SE it was possible to calculate 95% confidence intervals to inform the statistical significance of the comparison. Bucher ITCs were conducted using R version 3.6.1 or higher, based on methods described by Bucher et al.⁹⁵

B.2.9.2 Results of the indirect treatment comparisons

For the primary endpoint, benralizumab resulted in a statistically significant improvement in the proportion of participants in remission at both Weeks 36 and 48, compared with SoC. The OR for the primary remission definition was █████ (95% CI: █████, █████). The annualised RR for relapse was █████ (95% CI: █████, █████). For all other endpoints measured, results of the Bucher ITC were also in favour of benralizumab. The results which are incorporated in the economic analysis are presented in Table 19, with the remaining results presented in Appendix D.

Table 19: Summary of Bucher ITC Results

Outcome	Bucher ITC	Interpretation
Binary endpoint	OR (95% CI)	
Proportion of patients in remission at both Week 36 and Week 48 (main remission definition)	████ (████, █████)	The odds of patients being in remission at both Week 36 and Week 48 are █████ times higher for those receiving benralizumab compared with SoC
Rate endpoint	RR (95% CI)	
Annualised relapse rate	████ (████, █████)	Patients receiving benralizumab have a 43% lower risk of relapse over the course of the year compared with those receiving SoC

Abbreviations: CI: confidence interval; OR: odds ratio; RR: rate ratio

B.2.9.3 Uncertainties in the indirect treatment comparisons

The Bucher ITC was deemed appropriate as no adjustment for treatment effect modifiers was required, as validated by clinical experts.³ As detailed in Section B.2.9.1, the MANDARA and MIRRA trials were adequately comparable with regards to the study population, study design and outcome measurements.^{1, 34} Furthermore, clinical experts highlighted that the level of benefit demonstrated in the ITC for benralizumab versus SoC was similar to that demonstrated for mepolizumab (also an anti-IL-5 antibody) versus SoC (as shown in the MIRRA trial), supporting the results.³

Prior to analysis, clinical experts ranked a list potential treatment effect-modifiers. During the feasibility assessment, differences in these potential effect-modifiers were observed between the MANDARA and MIRRA study populations. NICE guidelines recommend conducting population-adjusted indirect comparisons when there is evidence suggesting that effect-modifiers are present and imbalanced between trial populations.⁹¹ Though cross-trial differences in ranked effect modifiers were considered by clinicians to not be meaningful (and hence a Bucher ITC was considered the primary indirect comparison approach), an anchored MAIC was conducted (methodology presented in Appendix D) in support of this submission and to further validate the results from the Bucher ITC.^{78, 91} The adjustments in the MAIC were made based on the pooled clinical expert rank-ordered list of treatment-effect modifiers.

In conclusion, the results of the MAIC were similar to those of the Bucher ITC i.e. a similar level of benefit was shown for benralizumab vs SoC irrespective of the approach adopted to generate the relative efficacy estimates. A scenario analysis with the relative efficacy informed by the MAIC is presented in Section B.3.10.3.

B.2.10 Adverse reactions

The safety and tolerability of benralizumab compared to mepolizumab in patients with EGPA was evaluated in the MANDARA trial and its open-label extension (OLE). Benralizumab at the higher EGPA dose was well tolerated and demonstrated a safety profile, consistent with that seen in previous asthma studies (SIROCCO [NCT01928771], CALIMA [NCT01914757], and BORA [NCT02258542]).⁹⁶⁻⁹⁸ There were no additional adverse drug reactions (ADR) identified. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA, version 26.0).

The safety analysis for both the double-blind (DB) period and the DB + OLE periods was performed using the Safety Analysis Set comprised of all patients who received at least one dose of the investigational product (IP). In the MANDARA trial the IP refers to benralizumab or mepolizumab. All safety analyses for the OLE period were performed using the OLE Analysis Set, which included all patients who received at least one dose of IP during the OLE period. When considering data from the OLE period, the treatment group “mepolizumab/benralizumab” includes patients who were in the mepolizumab arm during the DB period and then received benralizumab during the OLE period.

B.2.10.1 Extent of exposure

The duration of exposure to benralizumab and mepolizumab are presented in Table 20 for the DB period and Table 21 for the OLE period. In the DB period, the mean durations of IP administration were similar between both treatment groups in line with the mean duration of the DB period in each treatment group. In the OLE period, the mean durations of IP administration

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

were slightly longer in the mepolizumab/benralizumab group compared with the benralizumab group in line with the longer duration of the OLE period in the mepolizumab/benralizumab group.

Table 20: The duration of exposure to IP during the DB period (safety analysis set)

	Statistics	Benralizumab 30 mg (N=70)	Mepolizumab 300 mg (N=70)
Duration of IP administration ^a (days)	n	70	70
	Mean (SD)	████ (████)	████████
	Median (min, max)	██████████	██████████
	Total duration	████	████
Duration of DB period ^b (days)	n	70	70
	Mean (SD)	████████	████████
	Median (min, max)	██████████	██████████
	Total duration	████	████

Footnotes: ^a Duration of IP administration was calculated as last date of DB IP – first dose date of DB IP + 1 day.

^b Duration of study period (days) was calculated as follows: for patients who completed the DB period and had dosing in the OLE period: Date of the first OLE period dosing – Date of randomisation; for patients who early withdrew the study in the DB period: Date of early withdrawal – Date of randomisation + 1 day; for patients who early withdrew study treatment but completed the remainder of the DB period: Date of last DB visit – Date of randomisation + 1 day; and for patients who were lost to follow-up in the DB period: Date of the last contact – Date of randomisation + 1 day.

Abbreviations: CRF: case report form; DB: double-blind; IP: investigational product; max: maximum; min: minimum; N: number of patients in treatment group; n: number of patients in analysis; OLE: open-label extension; SD: standard deviation

Source: AstraZeneca MANDARA CSR, 2023⁸³

Table 21: The duration of exposure to IP during the OLE period (safety analysis set)

	Statistics	Benralizumab 30 mg (N=████)	Mepolizumab 300 mg switched to benralizumab 30 mg (N=████)
Duration of IP administration ^a (days)	n	████	████
	Mean (SD)	████████	████████
	Median (min, max)	██████████	██████████
	Total duration	████	████
Duration of OLE period ^b (days)	n	████	████
	Mean (SD)	████████	████████
	Median (min, max)	██████████	██████████
	Total duration	████	████

Footnotes: ^a Duration of IP administration was calculated as last date of OLE IP – first dose date of OLE IP + 1 day.

^b Duration of OLE period was calculated as last OLE visit date – first date of OLE IP + 1 day.

Abbreviations: IP: investigational product; max: maximum; min: minimum; N: number of patients in treatment group; n: number of patients in analysis; OLE: open-label extension; SD: standard deviation

Source: AstraZeneca MANDARA CSR, 2023⁸³

B.2.10.2 Adverse events (AEs)

Benralizumab was well tolerated by patients with EGPA, with no new safety concerns regarding AEs identified. Overall, AEs were reported by █ of patients in the benralizumab group during the DB + OLE periods and by █ of patients in the total benralizumab group reporting AEs while receiving benralizumab (Table 22).⁸³ The majority of these AEs were mild to moderate severity (for █% of participants in the benralizumab group with any AE in the DB period). There were fewer SAEs reported during the DB + OLE periods (█ in the benralizumab arm and █ of patients receiving benralizumab in the total group).⁸³

Table 22: AEs in any category during the DB and OLE period (safety analysis set)

AE category	Number (%) of patients	
	Benralizumab arm (N=70) ^a	Total benralizumab group (N=132) ^a
Any AE	█	█
Any SAE	█	█

Abbreviations: AE: adverse event; DB: double-blind; N: number of patients in treatment group; OLE: open-label extension; SAE: serious adverse event

Source: AstraZeneca MANDARA CSR, 2023⁸³

In the DB period, there was no clinically meaningful differences in the proportion of patients with AEs between the benralizumab and the mepolizumab groups (Table 23).¹ There was a relatively low number of patients reporting serious adverse events (SAEs) and AEs leading to discontinuation of treatment, as discussed in Section B.2.10.3. There were also no deaths during the DB period.¹

Table 23: AEs in any category during the DB period (safety analysis set)

AE category	Number (%) of patients	
	Benralizumab 30 mg (N=70) ^a	Mepolizumab 300 mg (N=70) ^a
Any AE	63 (90.0)	67 (95.7)
Any AE with outcome of death	0 (0.0)	0 (0.0)
Any SAE (including events with outcome of death)	4 (5.7)	9 (12.9)
Any AE leading to discontinuation of IP	0 (0.0)	2 (2.9)

Footnotes: ^a Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. Percentages are based upon number of patients in each treatment group within the Safety Analysis Set.

An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period). AEs were coded using MedDRA version 26.0

Abbreviations: AE: adverse event; DB: double-blind; IP: investigational product; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in treatment group; OLE: open-label extension; SAE: serious adverse event

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

The proportions of patients with AEs in the OLE period are presented in Table 24. There were no notable trends in the nature, frequency or intensity of AEs reported during the OLE period compared to the DB period. The proportions of patients with AEs or SAEs during the OLE period was similar between the benralizumab and mepolizumab/benralizumab group. A lower proportion

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

of AEs was reported during the OLE period compared to the DB period for the benralizumab group. There was one death in the mepolizumab/benralizumab group during the OLE period, as discussed in Section B.2.10.3, which was deemed not related to the interventions.¹

Table 24: AEs in any category during the OLE period (safety analysis set)

AE category	Number (%) of patients	
	Benralizumab 30 mg (N=■) ^a	Mepolizumab 300 mg switched to benralizumab 30 mg (N=■) ^a
Any AE	■	■
Any AE with outcome of death	■	■
Any SAE (including events with outcome of death)	■	■
Any AE leading to discontinuation of IP	■	■

Footnotes: ^aPatients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. The OLE period was defined from the first dose of OLE benralizumab 30 mg to the end of the study.

Abbreviations: AE: adverse event; IP: investigational product; N: number of patients in treatment group; OLE: open-label extension; SAE: serious adverse event

Source: AstraZeneca MANDARA CSR, 2023⁸³

AEs by system organ class and preferred term

The AEs reported during the DB period, with a preferred term (PT) frequency of >3% in either group, are presented in Table 25. There was a higher proportion of AEs reported in the mepolizumab group (87.1%) compared to the benralizumab group (72.9%). The most common AE was COVID-19, with 15 patients (21.4%) in the benralizumab group and 19 patients (27.1%) in the mepolizumab group with COVID-19 AEs during the DB period. Other common AEs included headache (17.1% of patients in the benralizumab group and 15.7% in the mepolizumab group) and arthralgia (17.1% of patients in the benralizumab group and 11.4% in the mepolizumab group).¹

In the OLE there were no clinically meaningful differences in the pattern and frequency of reported AEs by PT, compared to those reported for benralizumab during the DB period.

Table 25: Most common AEs in the DB period, with PT frequency of >3% (safety analysis set)

	Benralizumab 30 mg (N=70) (Exp=70.2 years) ^a		Mepolizumab 300 mg (N=70) (Exp=70.3 years) ^a	
PT	Number (%) of patients ^b	Event rate (per 100 PY) ^c	Number (%) of patients ^b	Event rate (per 100 PY) ^c
Any most common (frequency of > 3%) AE	51 (72.9)	■	61 (87.1)	■
COVID-19	15 (21.4)	■	19 (27.1)	■
Headache	12 (17.1)	■	11 (15.7)	■
Arthralgia	12 (17.1)	■	8 (11.4)	■
Nasopharyngitis	6 (8.6)	■	10 (14.3)	■

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Sinusitis	5 (7.1)	■	8 (11.4)	■
Fatigue	5 (7.1)	■	6 (8.6)	■
Bronchitis	5 (7.1)	■	5 (7.1)	■
Sinusitis bacterial	5 (7.1)	■	3 (4.3)	■
Upper respiratory tract infection	4 (5.7)	■	4 (5.7)	■
Influenza like illness	4 (5.7)	■	3 (4.3)	■
Nausea	1 (1.4)	■	6 (8.6)	■
Viral upper respiratory tract infection	1 (1.4)	■	6 (8.6)	■
Asthenia	6 (8.6)	■	0 (0.0)	■
Hypertension	1 (1.4)	■	5 (7.1)	■
Injection site bruising	2 (2.9)	■	4 (5.7)	■
Injection site pain	3 (4.3)	■	3 (4.3)	■
Oral candidiasis	2 (2.9)	■	4 (5.7)	■
Rash	4 (5.7)	■	2 (2.9)	■
Urinary tract infection	5 (7.1)	■	1 (1.4)	■
Back pain	2 (2.9)	■	3 (4.3)	■
Diarrhoea	2 (2.9)	■	3 (4.3)	■
Myalgia	4 (5.7)	■	1 (1.4)	■
Skin laceration	1 (1.4)	■	4 (5.7)	■
Tooth infection	3 (4.3)	■	2 (2.9)	■
Abdominal pain	0 (0.0)	■	4 (5.7)	■
Adrenal insufficiency	1 (1.4)	■	3 (4.3)	■
Asthma	1 (1.4)	■	3 (4.3)	■
Contusion	1 (1.4)	■	3 (4.3)	■
Muscle spasms	3 (4.3)	■	1 (1.4)	■
Pain in extremity	0 (0.0)	■	4 (5.7)	■
Rhinitis	1 (1.4)	■	3 (4.3)	■
Vomiting	1 (1.4)	■	3 (4.3)	■
Constipation	3 (4.3)	■	0 (0.0)	■
Herpes zoster	0 (0.0)	■	3 (4.3)	■
Osteopenia	0 (0.0)	■	3 (4.3)	■

Footnotes: ^a Exp = Total PY across all patients in DB period in the given treatment group.

^b Number (%) of patients with AEs, sorted on descending frequency for PT according to total frequency. Patients with multiple events in the same PT are counted only once for that PT. Patients with events in more than one PT are counted once in each of those PTs. Percentages are based upon number of patients in each treatment group within the Safety Analysis Set.

^c The event rate per 100 PY was defined as the number of patients with an AE divided by the total PY multiplied by 100.

An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period). Most common is defined as a total frequency of >3% in any treatment group. Adverse events were coded using MedDRA version 26.0.

Abbreviations: AE: adverse event; DB: double-blind; Exp: exposure; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in treatment group; OLE: open-label extension; PT: preferred term; PY: patient-years

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹ AstraZeneca MANDARA CSR, 2023⁸³

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Treatment-related AEs

In the benralizumab group, [REDACTED] of patients of AEs were assessed as being related to IP by the investigator compared to [REDACTED] in the mepolizumab group, with no clinically meaningful difference between these groups.⁸³ Relatedness of an AE was recorded on the Electronic Case Report Form (eCRF) for each AE by response to a prompt if there was a reasonable possibility the AE was caused by the IP. The most common treatment-related AEs are presented in Table 26.

Table 26: Most common treatment-related AEs in the DB period, with PT frequency of ≥2 patients in either group (safety analysis set)

PT	Benralizumab 30 mg (N=70) (Exp=70.2 years) ^a		Mepolizumab 300 mg (N=70) (Exp=70.3 years) ^a	
	Number (%) of patients ^b	Event rate (per 100 PY) ^c	Number (%) of patients ^b	Event rate (per 100 PY) ^c
Patients with any related AE	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Headache	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Fatigue	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Asthenia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injection site bruising	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injection site pain	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injection site erythema	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injection site haematoma	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injection site urticaria	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Footnotes: ^aExp = Total PY across all patients in DB period in the given treatment group. ^bNumber (%) of patients with AEs, sorted on descending frequency for PT according to total frequency. Each patient was represented by the maximum reported relationship for each PT. Any AE with missing relationship was considered as a related event. ^cThe event rate per 100 PY was defined as the number of patients with an AE divided by the total PY multiplied by 100.

Patients with events in more than one PT were counted once in each of those PTs. Percentages were based upon number of patients in each treatment group within the Safety Analysis Set. An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period). Adverse events were coded using MedDRA version 26.0.

Abbreviations: AE: adverse event; DB: double-blind; Exp: exposure; IP: Investigational product; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in treatment group; OLE: open-label extension; PT: preferred term; PY: patient-years

Source: AstraZeneca MANDARA CSR, 2023⁸³

AEs of interest

Based on the mechanism of action of benralizumab, AEs of interest included helminth infections and malignancy. No patients reported helminth infections during the DB or OLE period. There were three malignant neoplasm events (2 serious events of prostate cancer in the mepolizumab group and 1 non-serious event of marginal zone lymphoma in the benralizumab group) reported during the DB period. A total of 2 malignant neoplasm events (1 serious event of rectal cancer in the benralizumab group and 1 nonserious event of malignant melanoma in situ in the benralizumab group) were reported during the OLE period. None of the malignant neoplasm events reported were assessed as possibly related to the IP.⁸³

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.2.10.3 Deaths, SAEs and discontinuations

Deaths

There were no AEs with an outcome of death reported during the DB period. There was one death during the OLE period in the mepolizumab/benralizumab group due to a pulmonary embolism. This event was considered by the Investigator to be related to the patient's underlying conditions as the patients' medical history included deep vein thrombosis, surgical history of internal fixation, and open reduction of fracture. None of the events leading to the patient's death were considered by the Investigator to be related to the IP.¹

SAEs

There were no new safety concerns regarding the incidence of SAEs. During the DB period, 4 and 9 SAEs were reported in the benralizumab group and in the mepolizumab group, respectively. Out of 3 SAEs in the mepolizumab group, one was assessed by the Investigator as possibly related to IP, and 2 SAEs led to discontinuation of IP.^{1, 83} All patients in the benralizumab group and most patients in the mepolizumab group recovered from SAEs reported during the DB period. The SAEs that occurred during the DB period are presented in Table 27.

SAE data for benralizumab during the OLE period are presented in Appendix F.

Table 27: SAEs during the DB period (safety analysis set)

	Benralizumab 30 mg (N=70) (Exp=70.2 years)^a		Mepolizumab 300 mg (N=70) (Exp=70.3 years)^a	
SOC PT	Number (%) of patients^b	Event rate (per 100 PY)^c	Number (%) of patients^b	Event rate (per 100 PY)^c
Patients with any SAE	4 (5.7)	■	9 (12.9)	■
Infections and infestations	■	■	■	■
COVID-19	1 (1.4)	■	1 (1.4)	■
Appendicitis	0	■	1 (1.4)	■
Bronchitis	1 (1.4)	■	0 (0.0)	■
Streptococcal urinary tract infection	0 (0.0)	■	1 (1.4)	■
Wound infection	0 (0.0)	■	1 (1.4)	■
Hepatobiliary disorders	■	■	■	■
Cholangitis	0 (0.0)	■	1 (1.4)	■
Hepatic infiltration eosinophilic	0 (0.0)	■	1 (1.4)	■
Neoplasms benign, malignant and unspecified (including cysts and polyps)	■	■	■	■
Prostate cancer	0 (0.0)	■	2 (2.9)	■

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Nervous system disorders	████	█	████	█
Neuropathy peripheral	1 (1.4)	█	0 (0.0)	█
Syncope	1 (1.4)	█	0 (0.0)	█
Respiratory, thoracic and mediastinal disorders	████	█	████	█
Acute respiratory failure	0 (0.0)	█	1 (1.4)	█

Footnotes: ^a Exp = Total PY across all patients in DB period in the given treatment group.

^b Number (%) of patients with SAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency. Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than one PT were counted once in each of those PTs. Percentages were based upon number of patients in each treatment group within the Safety Analysis Set.

^c The event rate per 100 PY was defined as the number of patients with an SAE divided by the total PY multiplied by 100.

An SAE during the DB period was defined as a SAE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period). Serious AEs were coded using MedDRA version 26.0.

Abbreviations: AE: adverse event; DB: double-blind; Exp: exposure; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in treatment group; OLE: open-label extension; PT: preferred term; PY: patient-years; SAE: serious adverse event; SOC: system organ class

Source: AstraZeneca MANDARA CSR, 2023⁸³

Discontinuations of investigation product (IP)

No patients in the benralizumab group had adverse events leading to treatment discontinuation. There were two patients in the mepolizumab group with AEs that resulted in the discontinuation of IP during the DB period, as presented in Table 28, however these were not considered related to the IP.¹

AEs leading to discontinuation during the OLE were low and balanced between treatment groups. These data are presented in Appendix F.

Table 28: AEs leading to discontinuation of IP during the DB period (safety analysis set)

	Benralizumab 30 mg (N=70) (Exp=70.2 years)^a		Mepolizumab 300 mg (N=70) (Exp=70.3 years)^a	
SOC PT	Number (%) of patients^b	Event rate (per 100 PY)^c	Number (%) of patients^b	Event rate (per 100 PY)^c
Patients with any AE causing discontinuation of IP	0 (0.0)	0.0	2 (2.9)	2.8
Neoplasms benign, malignant and unspecified (including cysts and polyps)	████	█	████	█
Prostate cancer	0 (0.0)	0.0	2 (2.9)	2.8

Footnotes: ^a Exp = Total PY across all patients in DB period in the given treatment group.

^b Number (%) of patients with AEs, sorted on descending frequency for SOC and PT according to total frequency. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

^c The event rate per 100 PY was defined as the number of patients with an AE divided by the total PY multiplied by 100.

Adverse events were coded using MedDRA version 26.0

Abbreviations: AE: adverse event; DB: double-blind; Exp: exposure; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in treatment group; PT: preferred term; PY: patient-years; SOC: system organ class

Source: AstraZeneca MANDARA CSR, 2023⁸³

Other significant AEs

Other significant AEs, given the route of administration of benralizumab, include hypersensitivity events and injection site reactions. The overall proportions of patients with hypersensitivity AEs during the DB period were similar between the benralizumab group and the mepolizumab group, with ■ and ■ patients reporting hypersensitivity in these groups, respectively.⁸³ ■ hypersensitivity AEs in the benralizumab group and ■ hypersensitivity AEs in the mepolizumab group were assessed by the Investigator as possibly related to IP.⁸³ There were no cases of anaphylactic reactions reported during the DB period. No hypersensitivity AEs reported during the DB period were serious and none resulted in discontinuation of IP.

The overall proportions of patients with injection site reaction AEs during the DB period were low and similar between the benralizumab group and the mepolizumab group, with ■ and ■ patients reporting injection site reactions in these groups, respectively.⁸³ No injection site reaction AEs reported during the DB period were serious, most were transient in nature, and none resulted in discontinuation of IP. All injection site reaction AEs reported during the DB period were assessed by the Investigator as possibly related to IP and all were mild or moderate in intensity.

B.2.11 Ongoing studies

The MANDARA OLE investigating benralizumab for relapsing or refractory EGPA is ongoing at the time of this submission. Patients who completed the DB period were eligible to enrol onto the ongoing OLE phase of the study and could then receive benralizumab for at least one year; of the 140 patients who entered the MANDARA trial,¹ ■ entered the OLE. The OLE is investigating the same primary and secondary endpoints as the MANDARA trial, with a new data cut of results expected in 2025. Interim results for the OLE are presented in Appendix N. The trial is expected to complete in March 2026.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence

Clinical effectiveness

The key clinical effectiveness evidence for benralizumab in EGPA was provided by the MANDARA study, a Phase III, randomised, DB, active-controlled, parallel group, non-inferiority study comparing the efficacy and safety of benralizumab to mepolizumab in adults with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. The results of this study showed that benralizumab was efficacious at inducing remission in 58% of EGPA patients at Weeks 36 and 48, meeting the primary endpoint of MANDARA. Treatment with benralizumab also resulted in durable remission, with remission lasting for at least 24 weeks

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

in 57.1% of patients. Furthermore, the annualised relapse rate with benralizumab remained low (ARR of 0.5). In line with the induction of durable remission and avoidance of relapse, treatment with benralizumab had an OCS-sparing benefit, which is expected to prevent an increase in the incidence of OCS-related AEs and comorbidities. [REDACTED]

As the goal of EGPA treatment is to induce sustained remission and reduce dependence on high doses of OCS, this clinical evidence showed benralizumab to be an efficacious treatment option. Treatment with benralizumab would reduce the range of EGPA manifestations and symptoms, slow disease progression and prevent further organ damage.

Comparative efficacy of benralizumab versus SoC

The MANDARA trial provided a comparison of the efficacy of benralizumab versus mepolizumab, however mepolizumab is not a relevant comparator for this evaluation as it is not a reimbursed treatment option in the UK. As per the decision problem, the relevant comparator is SoC in UK clinical practice, consisting of OCS with or without IS. Given the lack of head-to-head trial informing the relative efficacy of benralizumab versus SoC in patients with EGPA, a Bucher ITC was conducted, using data for the benralizumab from the MANDARA trial and data for SoC arm (OCS with or without IS) from the MIRRA trial, anchored through the common comparator, mepolizumab.^{1, 34} Based on this analysis, benralizumab was associated with a statistically significant improvement in remission rates and a reduction in annualised relapse rates, in comparison to SoC.

Safety

Benralizumab at the higher EGPA dose in MANDARA was well-tolerated, with no new safety signals and an overall safety profile consistent with that observed for benralizumab in previous studies of severe asthma (SIROCCO [NCT01928771], CALIMA [NCT01914757] and ZONDA [NCT02075255]).⁹⁶⁻⁹⁸ There were similar proportions of AEs between treatment arms in MANDARA and the majority of these were mild or moderate in severity. There was a low rate of treatment-related adverse events, and a lower proportion of SAEs reported in the benralizumab treatment arm compared to the mepolizumab arm. There were no AEs or SAEs with an outcome of death during the DB period and only 28.6% of patients in the benralizumab arm had an IP-related AE, none of which resulted in the discontinuation of benralizumab.

B.2.12.2 Strengths and limitations in context to UK clinical practice

EGPA is a rare and poorly characterised disease, and as is common in the rare disease space, there was limited literature informing the evolution of the condition. Extensive work was undertaken by AstraZeneca to deepen understanding of the disease and generate a robust evidence base for benralizumab, in support of this submission. Whilst being the only RCT to inform the clinical evidence base for benralizumab, MANDARA was a high-quality trial demonstrating both internal and external validity.

Strengths

Internal validity of MANDARA

As discussed in Sections B.2.3, B.2.4 and B.2.5, the MANDARA trial was methodologically robust, with the results considered to be at a low risk of bias due to the following:

- Patients were randomised in a 1:1 ratio between treatment arms
- The trial was DB and therefore, participants and outcome assessors were appropriately blinded to treatment allocation

External validity of MANDARA

Results from MANDARA can be generalised to the UK population for the following reasons:

- MANDARA enrolled patients from the UK and five European countries (Belgium, France, Germany, Italy and the UK) anticipated to have similar demographics to the UK.⁸⁸ For example, 81.7% of England and Wales is White (2021 Census)⁹⁹ and ■■■% of the MANDARA population was White⁸³
- Clinical experts agreed that the baseline characteristics of patients from the MANDARA trial, and baseline treatment usage, were generalisable to patients in real-world practice in the UK, confirming the applicability of the trial results to the UK setting^{3, 83}
- MANDARA assessed the efficacy of benralizumab across a wide range of endpoints relevant to patients with EGPA and covering the spectrum of disease manifestations, including remission rates and durability of remission, relapse rates, OCS use, vasculitis activity and pulmonary function.
- During MANDARA, concomitant OCS and IS were allowed, in line with SoC in the UK, emulating the use of benralizumab in clinical practice

Limitations

MANDARA was a pivotal active-controlled phase III trial offering head-to-head evidence for benralizumab versus mepolizumab – a gold standard in evaluating the effectiveness of treatments.¹ However, given that mepolizumab is not a reimbursed treatment option in the UK, comparative efficacy estimates had to be generated for the relevant comparator for this submission; UK SoC comprising of OCS and IS.

An ITC, in the form of a Bucher ITC, was conducted to obtain relative efficacy estimates to inform the economic analysis. Clinical experts highlighted that the level of benefit demonstrated in the ITC for benralizumab versus SoC was similar to that demonstrated for mepolizumab (also an anti-IL-5 antibody) versus SoC (as shown in the MIRRA trial), supporting the results.^{3, 34}

As noted in Section B.2.9.3, an anchored MAIC was also conducted in support of this submission, in line with NICE's preference.⁹¹ The results of the anchored MAIC were used to inform a scenario analysis in the cost effectiveness model. The scenario analysis results (Section B.3.10.3) indicated a minor change to the ICER, therefore further validating the results of the Bucher ITC.

B.3 Cost effectiveness

Overview of the economic analysis

- A *de novo* economic analysis was conducted to assess the cost-effectiveness of benralizumab as an add-on to SoC treatment in adults with relapsing or refractory EGPA
- Comparator: A weighted average of the agents used in UK SoC; OCS (prednisolone) and IS therapies (e.g. azathioprine, mycophenolate mofetil and methotrexate)
- Model structure: A cohort-level, Markov state-transition model, which consisted of death and three alive health states which comprehensively captured the disease evolution: remission, stable disease and relapse.³ Given data limitations, it was not possible to implement the refractory and non-refractory health states as individual health states. Therefore, these were modelled as sub-states within a 'stable disease' health state
- Efficacy: MANDARA¹ (benralizumab efficacy) and Bucher ITC (benralizumab versus SoC relative efficacy)
- Health-state utilities: EQ-5D derived from the Adelphi DSP study.⁷⁴ Disutilities associated with OCS-related AEs were also incorporated in the analysis
- Cost categories: Drug acquisition costs, disease management costs and costs for treating OCS-related AEs

Overall evidence strategy

- The rarity of EGPA and lack of research and innovation in this space thus far means that there was limited literature and no prior cost-effectiveness evaluations to inform model inputs
- The evidence strategy adopted for this submission was in line with the NICE Real-World Evidence (RWE) framework, i.e. informing efficacy data from the RCT and other inputs using UK-relevant, EGPA-specific RWE¹⁰⁰

Key results

- The economic evaluation resulted in a deterministic ICER of £25,314/QALY gained
- The probabilistic ICER was consistent with the deterministic ICER, with a corresponding cost per QALY of £26,310
- The ICER was also robust to individual parameter uncertainty, with deterministic sensitivity analyses and scenario analyses having a minimal impact on the ICER

Benefits not captured in QALY

- Benralizumab is expected to prevent further organ damage, alleviating the symptom burden and improving HRQoL for patients
- Durable remission from treatment with benralizumab will allow patients to self-administer benralizumab at home, resulting in cost savings to the NHS and reducing disruption to patients' work and saving the time and cost of travel to hospitals

B.3.1 Published cost-effectiveness studies

A *de novo* SLR was conducted in June 2023 and updated in August 2024 to identify economic outcome data for patients with EGPA. Full details of the SLR search strategy, methodology and results are presented in Appendices G–I [cost-effectiveness studies (Appendix G), utility studies (Appendix H) and HCRU studies (Appendix I)].

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.2 Economic analysis

Features of the cost-effectiveness analysis

The cost-effectiveness analysis was conducted in line with the NICE reference case and the key features of the analysis and rationale are presented in Table 29.¹⁰¹

Table 29: Features of the base case economic analysis

Factor	Chosen values	Rationale
Population	Adults with relapsing or refractory EGPA, informed by the CPRD cohort of patients with EGPA ²	This population was modelled in line with the NICE final scope and the population in the MANDARA trial. The population demographics were informed by CPRD, as these are most representative of UK clinical practice – and therefore, most appropriate for the purpose of decision making in this evaluation ²
Intervention	Benralizumab	In line with the NICE final scope, benralizumab is the intervention being considered in this submission as an add-on treatment to SoC
Comparator	SoC (OCS with or without IS)	SoC in UK clinical practice consists of OCS with or without IS, as validated by clinical expert opinion ³ . Therefore, a weighted average of the most used agents was used as a comparator; OCS (prednisolone) and IS (azathioprine, mycophenolate mofetil and methotrexate). The treatment distribution was informed by CPRD data, which was validated by clinical expert opinion as being representative of UK clinical practice ^{3, 4}
Model structure	Markov model with the following health states: remission, non-refractory/refractory (modelled as sub-states of stable disease), relapse and a death state (Figure 9) There is an additional component to the model, referred to as the OCS sub-model (Figure 10) Figure 11 illustrates how the OCS sub-model was incorporated into the overarching economic model	These health states comprehensively capture the disease evolution, reflecting the relapsing-remitting nature of EGPA Given data limitations, it was not possible to implement the refractory and non-refractory health states as individual health states. Therefore, these were modelled as sub-states within a 'stable disease' health state (Section B.3.2.2) The effects of OCS use, namely chronic comorbidities and acute clinical events, were modelled using a sub-model to capture the impact on patient HRQoL and NHS costs ¹⁰² Further detail about the model structure is provided in Section B.3.2.2
Time horizon	Lifetime (maximum 60 years)	A lifetime horizon was chosen to reflect the chronic, lifelong nature of EGPA and is aligned with the NICE reference case ¹⁰¹

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Cycle length	28 days	A 28-day cycle length was chosen to align with the dosing schedule of benralizumab. For the simplicity of calculations, it was assumed there were exactly thirteen cycles in a year
Half cycle correction	Yes	A half-cycle correction was applied given that health state transitions may occur at any point during each cycle
Treatment waning effect	Waning of treatment effect from benralizumab has not been included in the model	The assumption of no treatment waning effect was consistent with the evaluation of benralizumab for severe eosinophilic asthma (TA565). ¹⁰³ Therefore, it can be inferred that similar durability of response would apply to EGPA, as validated by clinical expert opinion. ³ The treatment effects were assumed to cease immediately in patients who discontinued benralizumab
Analysis type	Cost-utility analysis	As per NICE reference case ¹⁰¹
Clinical effectiveness	MANDARA ¹ and Bucher ITC	Benralizumab arm: transition probabilities from MANDARA ¹ SoC arm: Bucher ITC outcomes applied to transition probabilities of benralizumab arm from MANDARA ¹
Cost categories included	• Drug acquisition costs • HCRU for disease management • OCS-related comorbidities and acute events	The acquisition costs of benralizumab and SoC were included in the model. The costs associated with management of EGPA were modelled specific to each health state to capture the costs to the NHS. Given the extensive OCS doses required to manage EGPA symptoms and consequently, the increased likelihood of developing comorbidities, the costs for chronic OCS-related comorbidities were included in the OCS sub-model analysis
Source of costs	eMIT, ¹⁰⁴ NHS reference costs, ¹⁰⁵ PSSRU unit costs ¹⁰⁶ and BNF ¹³	As per NICE reference case ¹⁰¹
Source of utilities	EQ-5D, reported by patients with EGPA as part of the Adelphi DSP study ⁷⁴	EQ-5D was not measured in MANDARA (mapped from SF-36); the mapped utility data from MANDARA did not accurately capture the patient experience of living with EGPA as validated by clinical experts ³ ; [REDACTED]; therefore Adelphi DSP study was conducted ⁷⁴ (Section B.3.4.4) Use of EQ-5D in line with NICE reference case ¹⁰¹
Annual discount rate for costs and outcomes	3.5%	As per NICE reference case ¹⁰¹
Perspective	NHS and PSS	As per NICE reference case ¹⁰¹

Abbreviations: BNF: British National Formulary; EGPA: eosinophilic granulomatosis with polyangiitis; eMIT: electronic marketing information tool; HCP: healthcare professional; HCRU: healthcare resource use; IS: immunosuppressants; ITC: indirect treatment comparison; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OCS: oral corticosteroids; PSS: personal social services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; TA: technology appraisal; UK: United Kingdom

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.2.1 Patient population

The population modelled in this cost-effectiveness analysis was adults with relapsing or refractory EGPA being treated with OCS, with or without IS. This was in line with the final scope from NICE for this evaluation and the population in the MANDARA trial.¹ Population demographics were derived from the CPRD cohort of patients with EGPA in England, to be most representative of UK clinical practice.² The baseline characteristics of individuals entering the cost-effectiveness model are summarised in Section B.3.3.1.

B.3.2.2 Model structure

Defining health states in EGPA

EGPA is a poorly characterised rare disease and there are no prior appraisals or published economic models given limited innovation in this space. Furthermore, given the limited research into EGPA to date, literature to help inform the evolution of the disease is scarce.

It was crucial for the economic analysis to capture the evolution of the disease and reflect the relevant health states as described in Section B.1.3.1. Consequently, extensive work was undertaken by AstraZeneca to deepen the understanding of the disease in support of this submission, as outlined in Table 30.

Table 30: Overview of workstreams conducted to deepen understanding of EGPA evolution

Workstream conducted	Rationale for conducting workstream
Systematic literature reviews	Identify any literature to help inform evolution of the disease and relevant health states in EGPA
Consultation with 3 patients with EGPA through an advisory board	Capture the patient-based experience of living with EGPA
Consultation with patients with EGPA through 8 in-depth interviews and with clinical experts through 4 in-depth interviews, as part of defining the health state descriptions for the purpose of conducting a UK-specific vignette study	Gain a deeper understanding of the relevant health states in EGPA, and characterise the symptom burden within each health state and the resulting impact on HRQoL, including psychological wellbeing and daily activities
Extensive consultation with clinical experts through 3 in-depth interviews	Validate the relevant health states inferred from interview-derived insights with patients and clinical experts, and confirm their definitions are consistent with what is observed in UK clinical practice

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; HRQoL: health-related quality of life; UK: United Kingdom

From the interviews with patients and clinical experts, it was evident that there are four distinct health states which are relevant: remission, non-refractory, refractory, relapse (Section B.1.3.1). Whilst remission and relapse have clear definitions, some patients experience disease that is not accurately described by either definition, and can broadly be characterised into two disease distinct sub-states with different, clinically meaningful profiles: non-refractory and refractory.³ These patients were often grouped into a 'stable disease' state in clinical trials. However, understanding of eosinophilic-driven diseases has progressed significantly since the pivotal

MIRRA and MANDARA trials first evaluated biologic therapies (mepolizumab and benralizumab) for EGPA.^{1, 34}

Currently, there is a clear focus on reducing patients' OCS exposure given the well characterised detrimental long-term health consequences as well as the negative impact on quality of life. In EGPA, the relevance of OCS exposure is particularly high considering that approximately 64% of patients require two or more OCS courses per year.¹⁵ This level of exposure is concerning, as evidence demonstrates that as few as 2–4 lifetime courses of OCS can lead to a significantly increased risk of adverse outcomes.^{32, 79, 107} Additionally, a cumulative OCS dose of ≥ 0.9 g has been shown to be linked to an 80% likelihood of an increase in glucocorticoid toxicity.⁷⁹ Considering that the mean cumulative dosage has been reported to be as high as 6.3 g in patients with EGPA across a mean follow-up duration of 21.7 months,⁸⁰ the majority of patients are likely to experience OCS-related AEs.

Given the high OCS doses required in EGPA, based on the hypereosinophilic nature of the condition, an OCS sub-model was incorporated in the Markov framework to capture the long-term health benefits and cost savings of OCS-sparing offered by benralizumab.¹⁰² Further detail is provided in the OCS sub-model section.

The definitions of the remission, refractory and relapse health states were aligned with the MANDARA trial.¹ The definition of the non-refractory health state was consistent with interpretation in UK clinical practice. All health state definitions were validated by clinical experts.³ Further information about each health state in reference to the economic analysis (with the refractory and non-refractory reflected as sub-states within a 'stable disease' health state) is provided below in Table 31.

Table 31: EGPA health state definitions in the cost-effectiveness analysis

Health state	Interpretation in UK clinical practice (Table 3)	Definition in economic model
Remission ²⁶	Absence of or mild clinical signs or symptoms attributable to active disease, including asthma and ENT manifestations	- BVAS = 0; AND - OCS dose ≤4 mg/day
Stable disease ³	Non-refractory Mild symptoms, deriving clinically meaningful benefit from being on a stable or tapered OCS dose Refractory Experiencing high symptom burden due to not responding to treatment and negative impact on mental wellbeing of patients, due to feelings of despair, anxiety and frustration they experience	Non-refractory - Stable OCS dose; OR - Tapered OCS dose related to EGPA Refractory - Not having achieved remission (BVAS = 0 and OCS dose ≤4 mg/day) at any time in the prior six months
Relapse ²⁶	Recurrence of clinical signs or symptoms attributable to active disease	- Active vasculitis (BVAS >0); OR - Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR - Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; - warranting any of the following: - An increased dose of OCS therapy to >4 mg/day prednisolone total daily dose; OR - An increased dose or addition of immunosuppressive therapy; OR - Hospitalisation related to EGPA worsening.

Abbreviations: ACQ-6: Asthma Control Questionnaire; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose and throat; IS: immunosuppressants; OCS: oral corticosteroids

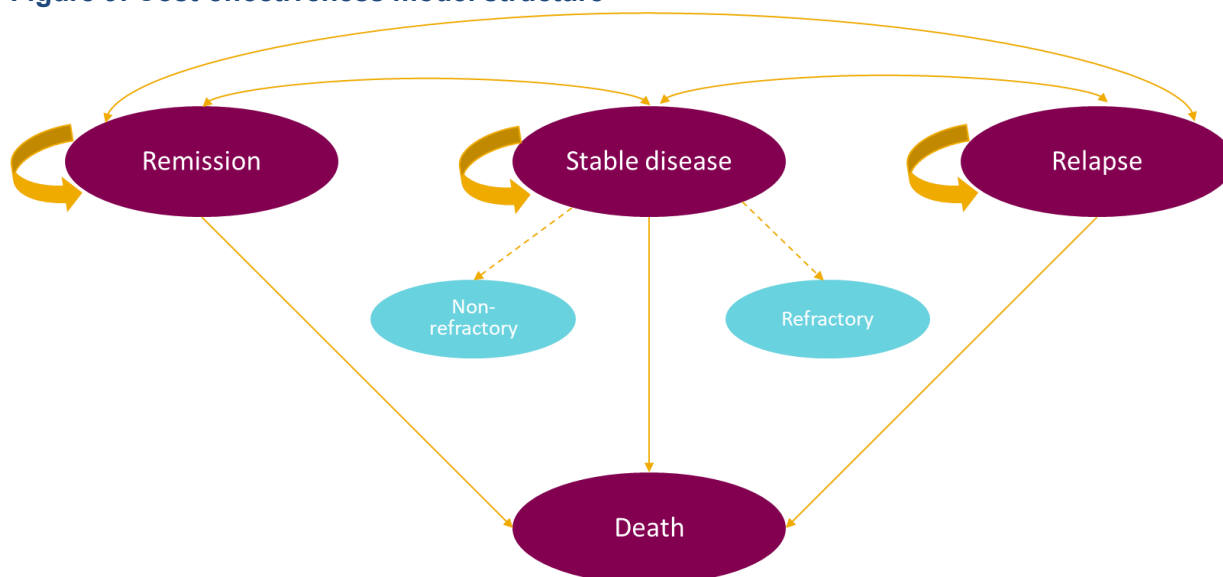
Overview of the model structure

As is commonly the case in the rare disease space, no prior models were identified by the economic SLR that characterised the natural history of EGPA or assessed the cost-effectiveness of treatments in EGPA (as described in Section B.3.1). Therefore, a *de novo* economic analysis was conducted to estimate the cost-effectiveness of benralizumab as an add-on treatment to SoC for adults with relapsing or refractory EGPA.³

The cost-effectiveness analysis was conducted using a cohort-level, Markov state-transition model built in Microsoft Excel®. A Markov framework was deemed appropriate to capture the relapsing-remitting disease course of EGPA, based on its suitability to capture the risk of disease over time as well as episodic events.³ Given the absence of prior NICE evaluations in patients with EGPA, an extensive review of NICE evaluations was undertaken into other related conditions to develop the optimal modelling approach. Evaluations in diseases such as vasculitis (TA308) and granulomatosis with polyangiitis (GPA) (TA825), were identified which are very distinct conditions with distinct pathogenesis making them poor proxies to inform any model inputs.^{77, 108} However, both diseases progress through remission/relapse states which were modelled using a Markov framework further supporting the approach adopted in this submission.

The cost-effectiveness model featured three mutually exclusive, alive health states – which comprehensively captured the disease evolution; namely remission, stable disease, relapse – as well as a death state (Figure 9). Due to the limited sample size in MANDARA (N=70 patients in the benralizumab arm), transition probabilities to and from the non-refractory and refractory health states from other health states could not be derived from the trial data. Given these data limitations, the refractory and non-refractory health states were modelled as sub-states within the stable disease health state. Further detail on this approach is provided in Section B.3.3.3.

Figure 9: Cost-effectiveness model structure



Footnotes: Purple boxes denote health states; blue boxes denote sub-states where patients were subject to sub-state specific utilities (Section B.3.4.4).

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis.

Patients entered the model in the stable disease health state (Section B.3.3.1), in accordance with the inclusion criteria of MANDARA (maintained on at least 7.5 mg of daily OCS, with or Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

without stable immunosuppressive therapy). Within any given cycle, patients were eligible to transition between any alive health state, or to the absorbing death state. The transitions possible within the model are described in further detail in B.3.3.2.

Health state occupancy was modelled at 4-week (28-day) intervals over the course of the lifetime horizon (maximum 60 years). Each health state was assigned a utility value, and costs associated with disease management; drug acquisition costs were also considered in the analysis. As discussed in Section B.1.3.4, OCS use can lead to an increased risk of a range of AEs and comorbidities. To capture the risks associated with OCS use, an OCS sub-model was incorporated in the Markov framework, which included disutilities and costs applied for each event, based on mean OCS dose per health state.¹⁰² In each cycle, the costs and utilities were multiplied by the proportion of patients in each health state to calculate the weighted costs and QALYs per health state. The weighted costs and QALYs per cycle were summed up over the entire model time horizon for each treatment arm, and the incremental costs and QALYs were subsequently calculated.

OCS sub-model

Capturing long-term health and economic benefits of OCS sparing in EGPA

As explained in B.1.3.3, a key component of SoC in EGPA is OCS required to manage symptoms. Given the hypereosinophilic nature of EGPA, high chronic doses of OCS are typically needed to achieve an acceptable level of symptom control. CPRD analysis identified mean daily doses of OCS ranging from 12.4 to 23.1 mg/day over time in the 5 years following EGPA diagnosis.⁴

Whilst OCS are effective anti-inflammatory agents, substantial evidence associates their use with increased risks for AEs, causing a high burden on the NHS, with OCS treatment shown to be one of the most common causes of hospitalisation due to AEs. Risks are increased even from short-term use, with cumulative lifetime OCS exposure being the main driving factor responsible for increased risk of AEs.¹⁰²

Therefore, to accurately model EGPA, it was crucial to capture the range of AEs (comorbidities and acute events) and reflect the costs and HRQoL decrements associated with each of these events. Correspondingly, it was also important to capture the long-term benefits of OCS-sparing agents, such as benralizumab, and capture the cost savings and positive implications on HRQoL associated with reducing the incidence of chronic and acute OCS-related AEs.

Approach used in prior NICE appraisals

In the recent NICE technology appraisals for tezepelumab (TA880) and benralizumab (TA565), biologics recommended for the treatment of severe asthma and severe eosinophilic asthma, respectively, the effects of long-term OCS maintenance were considered to impact HRQoL and HCRU through the risk of developing OCS-related comorbidities.^{103, 109} In these models, 10 AEs commonly associated with OCS exposure were included as acute AEs with incidence data based on patients' average daily dose in that model cycle. However, during the tezepelumab evaluation, expert review noted that the full effects of OCS-sparing were unlikely to be fully captured within the model submitted in that evaluation. This underestimation was primarily due to the underlying assumption that all AEs were acute events incurring a one-off incidence cost and QALY loss, which underestimated the long-term costs and QALY losses from conditions such as T2DM, cardiovascular disease and osteoporosis.

Company evidence submission for benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Approach used in this submission

To address the limitation of the prior approach used to model OCS sparing, and better inform healthcare decision making, this submission utilised a recently published modelling approach designed to more comprehensively capture the health economic outcomes related to reducing OCS use. The approach was referred to as the “OCS sub-model” and comprised of a Markov model structure to model the most common chronic comorbidities and acute events resulting from OCS use, and the associated costs and impact on HRQoL, in alignment with the model published by Gibson et al. 2024 (Figure 10).¹⁰²

Patients could enter the model in either the event-free health state or any of the chronic disease health states based on baseline population characteristics, presented in Section B.3.3.1, with patients developing increasingly multimorbid disease as they accumulated OCS dose over time.

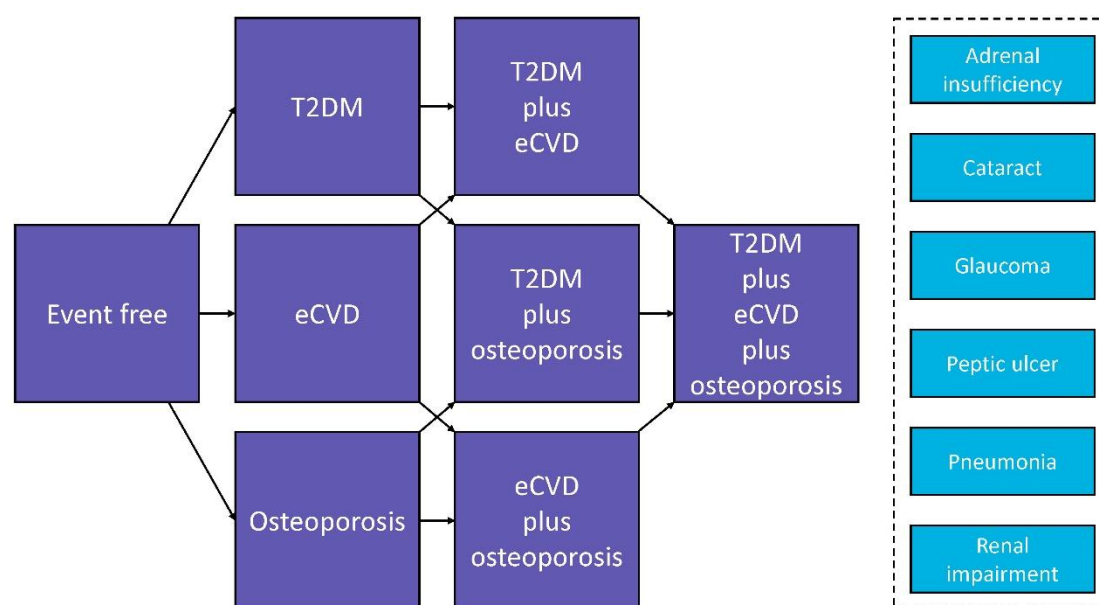
Three chronic comorbidities (in purple in Figure 10) were included in the sub-model: T2DM, established cardiovascular disease (eCVD) and osteoporosis. These were chosen as they were the key drivers of morbidity and mortality from OCS-related AEs impacting patient HRQoL and NHS costs.¹⁰² The definition of eCVD included cardiovascular events for myocardial infarction and heart failure, and cerebrovascular disease including stroke.

As well as developing chronic comorbidities, patients were at a risk of developing acute AEs (in blue in Figure 10). These were additional AEs that are commonly associated with OCS in the literature but are considered as “one-off” events captured in a simplified manner as acute events, driven by incidence. These included adrenal insufficiency, cataract, glaucoma, peptic ulcer, pneumonia, and renal impairment. Since these events were more acute in nature, they were modelled for the duration of one cycle length (28 days).

No OCS-related mortality was captured in the OCS sub-model as all-cause mortality was captured in the EGPA model structure, which would already inherently capture the effects of chronic OCS use on the risk of death. As explained above, the OCS sub-model only captured the costs and impact on HRQoL associated with OCS exposure. Further details on this approach are provided in Section B.3.3.6.

The overarching model structure, including the OCS sub-model was validated by clinical and health economic experts; all experts agreed the modelling approaches were appropriate balancing the need to reflect the evolution of the disease with simplicity considering the available data.^{3, 78}

Figure 10: OCS sub-model structure



Footnotes: Purple boxes relate to chronic disease health states; blue boxes relate to acute events.

Abbreviations: eCVD: established cardiovascular disease; OCS: oral corticosteroid; T2DM: type-2 diabetes mellitus

NB: In the Gibson publication, adrenal insufficiency was effectively modelled as a fourth chronic comorbidity (alongside T2DM, eCVD and osteoporosis).¹⁰² Adrenal insufficiency was not included in the OPRI study, therefore the parametrisation of incidence as a function of cumulative OCS was unknown.¹¹⁰ In light of this, a simplified approach was adopted to model adrenal insufficiency as an acute event in the OCS sub-model; the incidence of the event was informed by a targeted literature search, a one-off cost was applied in the cycle of incidence, and no disutility was applied as a conservative assumption, in absence of data reported from Gibson et al. publication

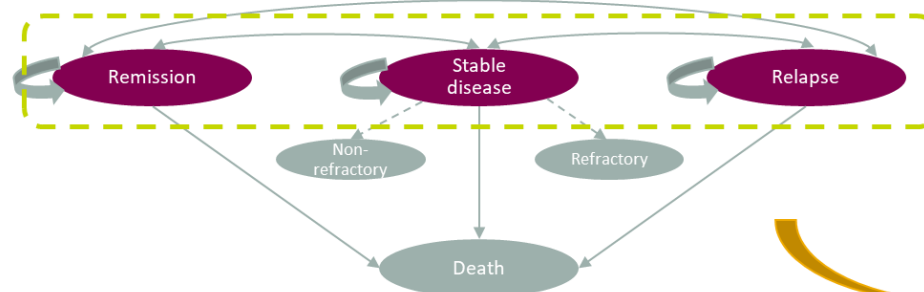
The OCS sub-model was incorporated into the overall Markov model, as shown in Figure 11. Transitions through the OCS sub-model (i.e. cumulative OCS doses required to experience an OCS-related AE) are described in Section B.3.3.6.

Figure 11: How the OCS sub-model was incorporated into the overarching economic model

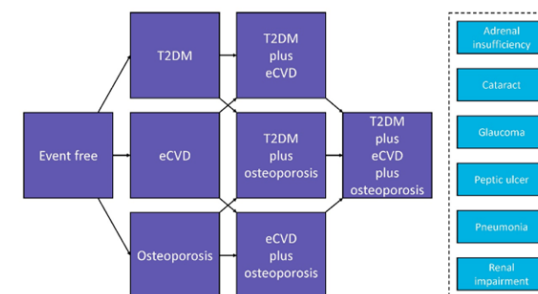
Patients enter the model;
baseline characteristics as per
CPRD

- Remission, stable disease and relapse health states have mean dose OCS/day, informed from CPRD
- For each 28-day cycle that patients resided in a health state, they accumulated 28 times the mean daily dose attributed to that health state*
- A weighted mean dose for the entire cohort (across remission, stable disease and relapse) was then derived to inform the risk of developing chronic disease and acute events

* daily dose assumed constant over the course of one cycle



Rate of developing chronic disease and acute events informed by OPRI RWE study[#]



t=0

NB: Only 86.2% of patients are subject to the 'OCS module' as only 86.2% of patients are on OCS, based on CPRD

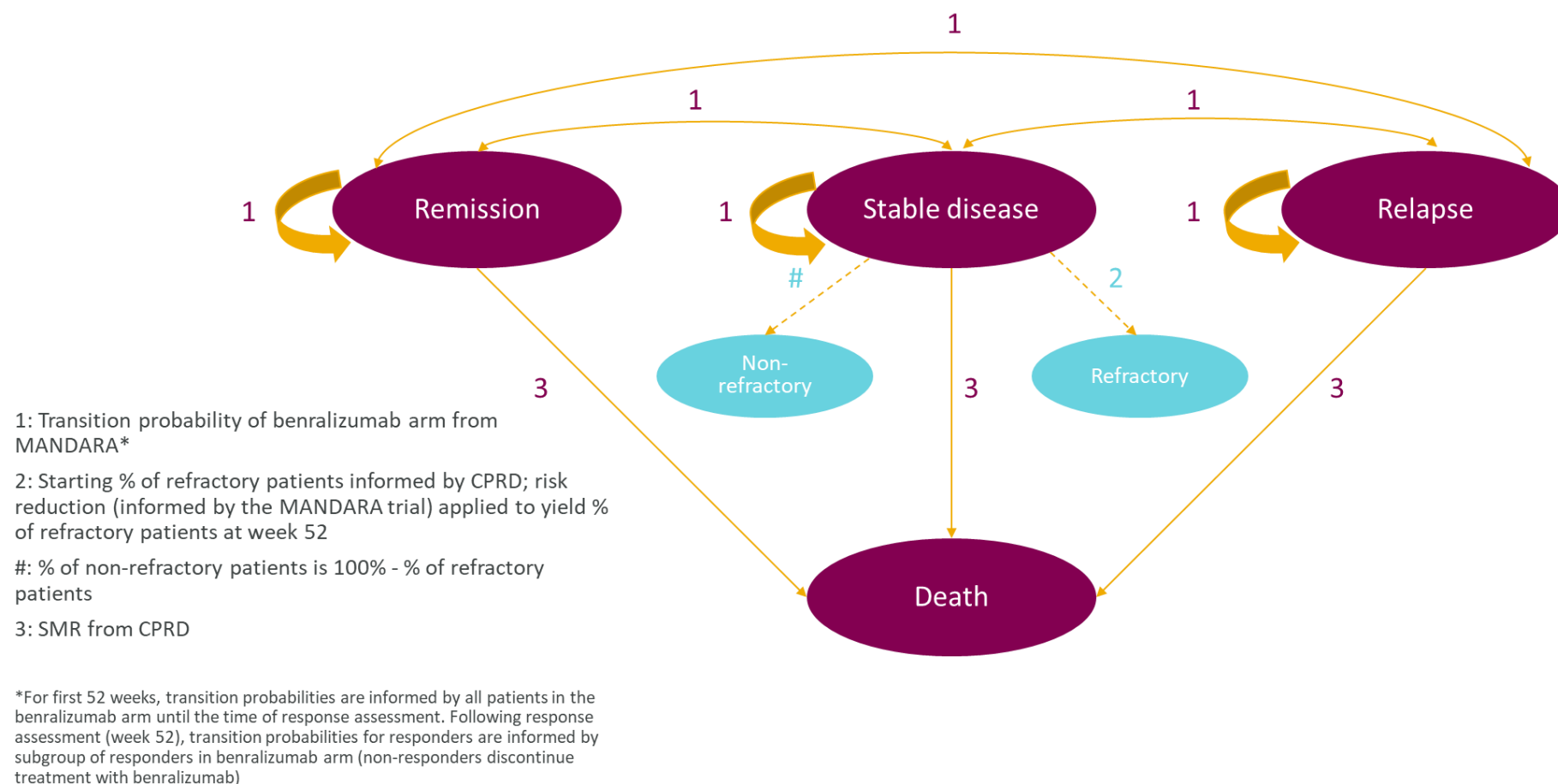
- As time progresses, the total OCS exposure accumulates, thus resulting in a cumulative increased risk of developing a chronic disease and acute event
- Patients can develop a chronic disease and experience an acute event at the same time
- If a patient discontinues OCS, their risk of developing a chronic disease and an acute event plateaus

Footnotes: [#] Rate of developing chronic diseases and acute events in the general population informed by OPRI RWE study; the rate of EGPA patients developing chronic diseases and acute events is informed by applying HR (based on cumulative OCS dose) to rate of developing chronic diseases in the general population; HR informed by OPRI RWE study; the OPRI RWE study is a matched historical cohort study conducted using the OPCR and the CPRD database; The risk of patients developing acute events (e.g. pneumonia, cataracts, sleep apnoea and renal impairment) does not increase as patients develop more comorbid conditions (T2DM, eCVD and osteoporosis) based on limited evidence to parameterise the required 18 model inputs and given the likely minor impact on results, this was excluded

Abbreviations: CPRD: Clinical Practice Research Datalink; eCVD: established cardiovascular disease; EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroids; OPRI: Observational and Pragmatic Research Institute; RWE: real-world evidence; t=0: time at start; T2DM: type-2 diabetes mellitus

Figure 12 and Figure 13 illustrate key data inputs used to parameterise the model structure for the benralizumab arm and the SoC arm.

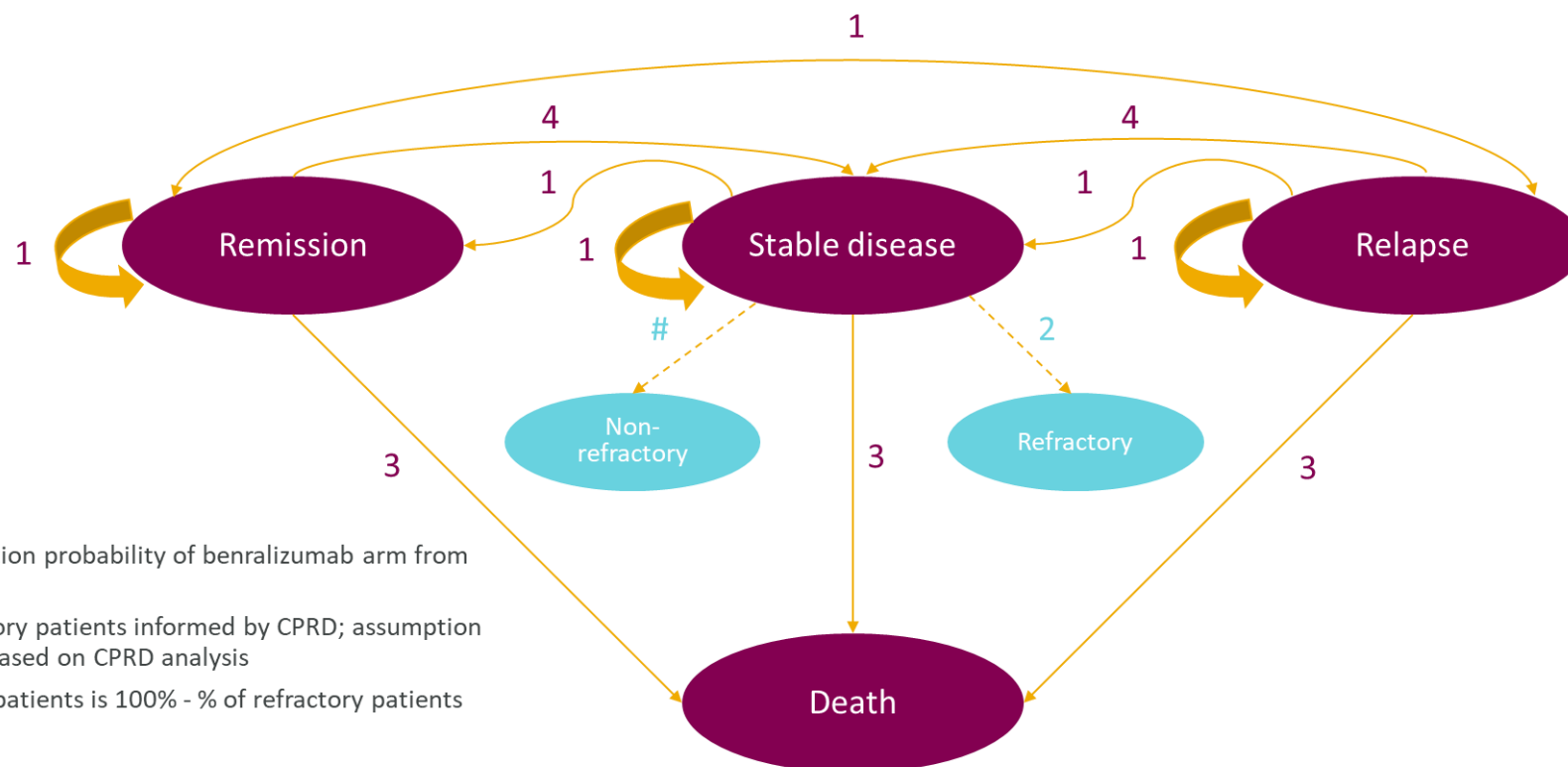
Figure 12: Model structure parameterisation, by treatment arm – benralizumab arm



Abbreviations: CPRD: Clinical Practice Research Datalink; SMR: standardised mortality ratio

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Figure 13: Model structure parameterisation, by treatment arm – SoC arm



1: ITC applied to transition probability of benralizumab arm from MANDARA*

2: Starting % of refractory patients informed by CPRD; assumption that % stays constant based on CPRD analysis

#: % of non-refractory patients is 100% - % of refractory patients

3: SMR from CPRD

4: Transition probabilities assumed equivalent to benralizumab §

*No response assessment for SoC arm; transition probabilities stay constant throughout time horizon

§ ITC has 2 endpoints; odds of remission and annualised relapse rate; no data to inform transition probabilities to stable disease

Abbreviations: CPRD: Clinical Practice Research Datalink; ITC: indirect treatment comparison; IPD: individual patient data; SMR: standardised mortality ratio; SoC: standard of care

B.3.2.3 Intervention technology and comparators

Intervention: Benralizumab

The intervention considered in the cost effectiveness analysis was benralizumab as an add-on treatment to SoC. The model included the dose of benralizumab anticipated to be indicated for EGPA: 30 mg, Q4W by SC injection. As benralizumab is anticipated to be indicated as an add-on treatment for EGPA, “benralizumab” in this submission refers to treatment with benralizumab in addition to SoC.

Comparators

As discussed in Section B.1.1, the appropriate comparator for this submission was a weighted average of the most used agents for the management of EGPA in UK clinical practice. Clinical guidelines and clinical expert opinion indicate that the most used agents to induce and maintain remission for EGPA are OCS and IS (e.g. methotrexate, azathioprine and mycophenolate mofetil) and therefore, these are considered to form SoC in the UK.^{2, 3} The treatment distribution was informed by Clinical Practice Research Datalink (CPRD) data, which was validated by clinical expert opinion as being representative of UK clinical practice.^{3, 4}

The comparator treatments are summarised in Table 32.

Table 32: Comparator treatments in the cost-effectiveness analysis

Treatment	Agent	Route	Distribution within regimen	Recommended dose (SmPC)	Modelled dose	Source
Benralizumab	Benralizumab	SC injection	100%	30 mg Q4W	30 mg Q4W	MANDARA ¹
OCS	Prednisolone	Oral	86.2%	The dosage for the model cycle is 1 mg. The initial dosage can vary from 5–60 mg daily in divided doses. This dose can be reduced within a few days but may need to be continued for several weeks or months. A maintenance dose of 2.5–15 mg daily is recommended but higher doses may be required ¹¹¹	[REDACTED]	CPRD ²
IS	Azathioprine	Oral	32.5%	For adults, a dose of up to 5 mg/kg body weight per day should be given on the first day of treatment. The maintenance dosage is usually 1–4 mg/kg body weight per day ¹¹²	[REDACTED]	
	Mycophenolate mofetil	Oral	14.8%	The recommended dose is 1.5 g administered twice daily ¹¹³	[REDACTED]	
	Methotrexate	Oral	17.5%	Dosages are based on the patient's body weight or surface area ¹¹⁴	[REDACTED]	

Abbreviations: IS: immunosuppressants; mg: milligram; OCS: oral corticosteroids; SC: subcutaneous; Q4W: every 4 weeks

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.3 Clinical parameters and variables

Evidence strategy

- The rarity of EGPA and lack of research and innovation in this space thus far means that there was limited literature and no prior CE evaluations to inform model inputs
- The main clinical evidence supporting the use of benralizumab as an add-on treatment in patients with relapsing or refractory EGPA is the pivotal, Phase III MANDARA trial which had a methodologically robust study design in line with the decision problem, making it an appropriate source of clinical data for the model.¹ However, mepolizumab is not reimbursed in the UK for EGPA and is not a comparator, as specified in the NICE final scope
- Therefore, an ITC was conducted, in the form of a Bucher ITC, to inform the relative efficacy of benralizumab versus SoC. These findings were summarised in Section B.2.9
- The evidence strategy adopted for this submission was in line with the NICE RWE framework, i.e. informing efficacy data from the RCT and informing other inputs using UK-relevant, EGPA-specific RWE¹⁰⁰
- Extensive clinical validation was conducted to ensure inputs reflected UK clinical practice

A summary of sources used to inform clinical parameters in the cost-effectiveness analysis is presented in Table 33.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 33: Summary of clinical data sources informing the cost-effectiveness analysis

Input	Source	Rationale
Baseline population demographics	CPRD ²	This is a large, UK-based dataset of patients with EGPA, representative of UK clinical practice
Baseline comorbidity distribution	CPRD ²	This is a large, UK-based dataset of patients with EGPA, representative of UK clinical practice
Transition probabilities (benralizumab arm)	MANDARA ¹	Pivotal evidence source for the efficacy of benralizumab
Transition probabilities (SoC, relative to benralizumab)	Bucher ITC, Section B.2.9	In the absence of head-to-head evidence for the effectiveness of benralizumab versus the decision problem specified comparator, SoC, which includes OCS with or without IS treatment, an ITC was required. No transition probabilities were modelled for the sub-states of the stable disease health state: refractory and non-refractory
Response assessment conducted at 52 weeks	MANDARA ¹	The response assessment at 52 weeks was consistent with the length of the MANDARA trial and the recommended use of benralizumab in severe asthma. ^{1, 108} Clinical expert opinion validated that benralizumab would be prescribed in the same manner for EGPA in UK clinical practice ²
Health state-specific SMR	CPRD ²	No deaths occurred in the benralizumab arm of MANDARA and no literature was identified to inform mortality risk. ¹ Therefore, these inputs were derived from CPRD analysis to capture the risk of death and how it varied by health state. These are representative of UK clinical practice.
Discontinuation of benralizumab	Mid-point of range of sources	Discontinuation rate of benralizumab in MANDARA was validated by clinical experts as being unusually low and not representative of a real-world setting; ³ therefore, alternative sources were explored
Discontinuation of OCS with benralizumab	MANDARA ¹	Pivotal evidence source for the efficacy of benralizumab
Discontinuation of OCS with SoC	Assumption	Following guideline-directed management of EGPA which is primarily based on chronic high-dose OCS, it was assumed that no patients could discontinue SoC as validated by clinical experts ³

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

OCS-related adverse events	Published literature sources	Benralizumab-related AEs were not included in the cost-effectiveness analysis given the low incidence of serious AEs observed in MANDARA, consistent with the previous model evaluating benralizumab for severe asthma (TA565). ¹⁰³ Chronic disease and acute AEs related to OCS treatment were captured via the OCS sub-model

Abbreviations: AE: adverse event; CPRD: Clinical Practice Research Datalink; EGPA; eosinophilic granulomatosis with polyangiitis; ITC: indirect treatment comparison; OCS: oral corticosteroids; RWE: real-world evidence; SoC: standard of care; SMR: Standardised mortality ratio

NB: Patients with GPA, another vasculitic disease, have avacopan as a reimbursed treatment option.⁸³ In this submission, no inputs from the avacopan technology evaluation (TA825) were utilised. Despite falling under the same umbrella of vasculitis, GPA and EGPA are different diseases, which present with different pathogeneses and clinical manifestations, and therefore are not similar.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.3.1 Baseline characteristics

Demographic characteristics

The characteristics of patients entering the model were derived from CPRD, a large, UK-based cohort of patients with EGPA, therefore representative of the target population (Table 34).²

Table 34: Inputs for baseline characteristics

Demographics	Mean	SE	Source
Age (years)	████	████	CPRD ²
Percentage of males	████	████	

Abbreviations: SE: standard error

OCS-related comorbidities (OCS sub-model)

With regards to the OCS sub-model, patients could start in the event-free state or any of the baseline chronic disease health states based on population characteristics, with patients developing increasingly multimorbid disease as they accumulated OCS dose over time. The distribution of baseline comorbidities is presented in Table 35, and were derived from CPRD.²

Table 35: Inputs for comorbidities at baseline

Comorbidities	Mean	SE	Source
Proportion with T2DM without eCVD and osteoporosis	████	████	CPRD ²
Proportion with eCVD without T2DM and osteoporosis	████	████	
Proportion with osteoporosis without T2DM and eCVD	████	████	
Proportion with T2DM and eCVD without osteoporosis	████	████	
Proportion with T2DM and osteoporosis without eCVD	████	████	
Proportion with eCVD and osteoporosis without T2DM	████	████	
Proportion with T2DM and eCVD and osteoporosis	████	████	

Abbreviations: eCVD: established cardiovascular disease; SE: standard error; T2DM: type-2 diabetes mellitus

B.3.3.2 Transition probabilities and response assessment

Patients entered the model in the stable disease health state, in line with the MANDARA inclusion criteria (stable dose of OCS of ≥ 7.5 mg/day for at least four weeks prior to randomisation and stable dose of IS for the four weeks prior to randomisation). Following model entry, transition probabilities determined how likely participants were to move between health states. Transition probabilities were treatment-specific, capturing the effect of benralizumab versus SoC in the achievement of durable remission.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

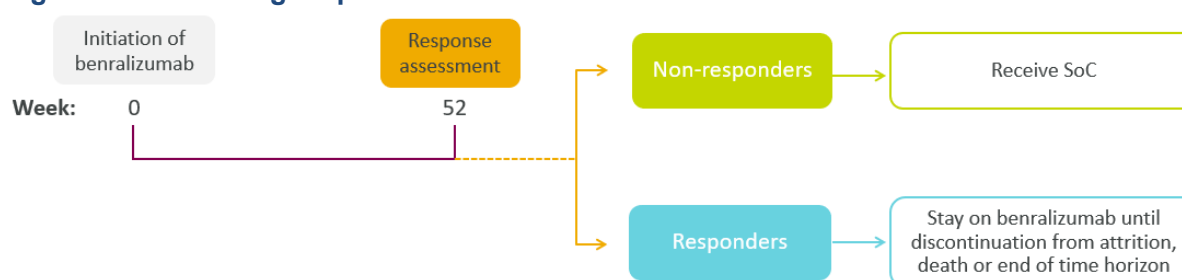
Response assessment

At 52 weeks, patients in the benralizumab arm of the model were assessed for their treatment response. The definition of response was consistent with the primary endpoint of the MANDARA trial, i.e. BVAS=0 and an OCS dose ≤ 4 mg/day.¹ The probability of response was informed by MANDARA (Table 36). Responders continued to receive benralizumab treatment whilst non-responders discontinued benralizumab treatment (Figure 14), and the movement through health states pre- and post-assessment is described in the section below.

As mentioned in Table 33, the response assessment at 52 weeks was consistent with the length of the MANDARA trial, the recommended use of benralizumab in severe asthma, and in line with the anticipated use of benralizumab in EGPA in UK clinical practice.³

No response assessment was conducted for the SoC arm, in line with UK clinical practice.

Figure 14: Assessing response to benralizumab



Abbreviations: SoC: standard of care

Table 36: Inputs for treatment response with benralizumab

Parameter	Mean	SE	Source
Time of response assessment (weeks)	52	NA	Clinical expert opinion ³
Probability of achieving response upon assessment	████	████	MANDARA

Abbreviations: NA: not applicable; SE: standard error

Intervention: benralizumab

Prior to the response assessment, transition probabilities in the benralizumab arm of the model were derived from all patients in the benralizumab arm of MANDARA up until the time of response assessment (Table 37). Transition probabilities were derived using 28-day transition count data assuming last observation carried forward (i.e., patients were assumed to remain in a health state until an observation indicating they had moved elsewhere). Transition counts had a multinomial likelihood, which had a flat Dirichlet prior distribution using Gibbs sampling to obtain the posterior probability distribution of the health state transition matrix.¹¹⁵

Following response assessment, patients who were identified as being responsive to benralizumab continued treatment; transition probabilities for responders were then informed only by the subgroup of responders in the benralizumab arm of MANDARA, following the methods specified above. It was assumed that responders' transition probabilities remained constant throughout the remainder of the lifetime horizon of the model as benralizumab exhibits

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

no treatment-waning effect, as validated by clinical expert opinion.³ Patients who were unresponsive to benralizumab treatment immediately discontinued benralizumab and were modelled as per the efficacy of SoC.

The transition probabilities for patients receiving benralizumab in the economic model are presented in Table 37 with clinical expert opinion supporting the notion that responders will have an uplift in efficacy.³

Table 37: Transition probabilities in the benralizumab arm

Health state transition	Pre-response assessment		Responders	
	Mean	SE	Mean	SE
Remission → Remission	████	████	████	████
Remission → Stable disease	████	████	████	████
Remission → Relapse	████	████	████	████
Stable disease → Remission	████	████	████	████
Stable disease → Stable disease	████	████	████	████
Stable disease → Relapse	████	████	████	████
Relapse → Remission	████	████	████	████
Relapse → Stable disease	████	████	████	████
Relapse → Relapse	████	████	████	████

Abbreviations: SE: standard error

Comparator: SoC

In the absence of head-to-head clinical trials assessing the efficacy of benralizumab versus SoC in patients with EGPA, a Bucher ITC was conducted, as described in Section B.2.9. To derive the transition matrix for the SoC arm, the comparative efficacy from the Bucher ITC (Table 38) was applied to the transition matrix for the benralizumab arm presented above. The transition probabilities for patients receiving SoC in the economic model are presented in Table 39.

For the SoC arm of the model, as a conservative assumption, the probability of entering the stable disease health state was assumed equivalent to that in the benralizumab arm in the absence of comparative effectiveness evidence for such transitions from the Bucher ITC.

Table 38: Relative efficacy of benralizumab versus SoC

Parameter	Mean	SE (log) ^a
OR for the odds of remission (relative to SoC)	████	████
RR for the rate of relapse (relative to SoC)	████	████

Footnotes: ^aThe SE used in the model was derived from the 95% CI around the mean parameter and log-transformed for synthesis with the log-normal distribution.

Abbreviations: CI: confidence interval; OR: odds ratio; RR: rate ratio; SE: standard error

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 39: Transition probabilities in the SoC arm

Health state transition	
Remission → Remission	████
Remission → Stable disease	████
Remission → Relapse	████
Stable disease → Remission	████
Stable disease → Stable disease	████
Stable disease → Relapse	████
Relapse → Remission	████
Relapse → Stable disease	████
Relapse → Relapse	████

Footnote: No SEs are presented with these transition probabilities because the SE was already captured in the ITC outcomes

Abbreviations: ITC: indirect treatment comparison; SE: standard error; SoC: standard of care

B.3.3.3 Informing the proportion of patients in the refractory sub-state, by treatment arm

As described in Section B.3.2.2, the refractory and non-refractory health states were modelled as sub-states within the stable disease health state. The refractory and non-refractory sub-states were captured in the model by allocating a proportion of patients in each sub-state, by treatment arm. The proportion of refractory patients was derived from CPRD data, and the approach is outlined below. The proportion of non-refractory patients was calculated as 100% minus the proportion of refractory patients as they were all-encompassing within the 'umbrella' term of stable disease. The refractory and non-refractory sub-states were associated with specific health-state utilities, akin to the other health states, remission and relapse.

The following subsections describe the approach to inform the proportion of patients in the refractory sub-state by treatment arm.

SoC arm

- No data were available from the MANDARA trial to inform the SoC arm, as this was not the comparator in the trial¹
- Therefore, an analysis was undertaken by AstraZeneca using the CPRD dataset. The analysis determined that, of the cohort who receive UK SoC, █████% had refractory disease and that this proportion stayed constant over the 5 years of the study. A brief overview of this CPRD study is included below:²
 - The study was a 5-year longitudinal retrospective observational cohort study conducted using the Clinical Research Practice Datalink (CPRD) Aurum primary care database with linkage to the Hospital Episode Statistics inpatient admitted

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

patient care (HES APC), HES outpatient (HES OP), accidents and emergencies (HES A&E) records and the ONS death data from the UK

- Cases of EGPA were identified from the CPRD medical records and the HES APC records
- The CPRD study included all patients with EGPA, and was representative of the EGPA patient population in England and the wider UK
- Therefore, to remain consistent with the CPRD data, the economic analysis considered █% of patients as having refractory disease within the stable disease health state, and this proportion was constant over the time horizon of the analysis, as validated by clinical experts.³

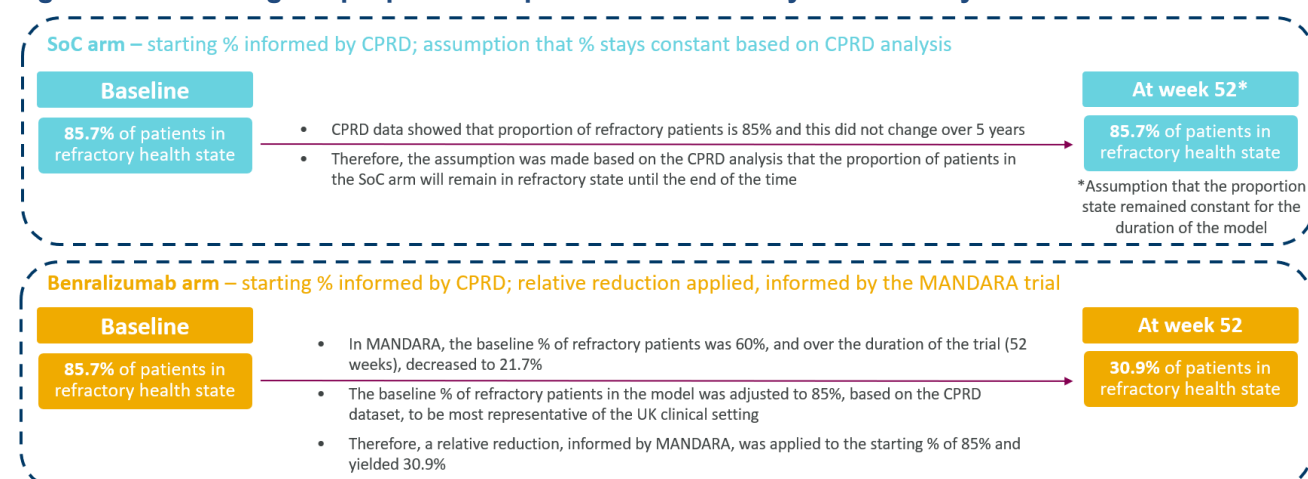
Benralizumab arm

- Individual patient data (IPD) were available from the pivotal trial, MANDARA¹
 - IPD indicated that at baseline, █% of patients had refractory disease in the benralizumab arm
 - By end of the trial (52 weeks duration), █% of patients had refractory disease in the benralizumab arm, which represented a █% risk reduction
- To ensure consistency across treatment arms in the economic model, the starting proportion of refractory patients in the benralizumab arm was also sourced from CPRD (█%), to be most representative of UK patients
- The risk reduction (informed by MANDARA) was applied to the starting proportion to yield the █% patients with refractory disease at Week 52

The approach is summarised in Figure 15 below. In addition, to support the model assumptions, these proportions were validated with clinical experts who confirmed they were reflective of UK clinical practice.³

The starting proportions of patients in the sub-states was varied by +/- 5% in scenario analyses. (Section B.3.10.3). The same assumptions from the base case were applied i.e., the relative reduction informed by MANDARA was applied to the benralizumab arm, and the proportion stayed constant in the SoC arm.

Figure 15: Informing the proportion of patients in refractory sub-state by treatment arm



Abbreviations: CPRD: Clinical Practice Research Datalink; SoC: standard of care

B.3.3.4 Mortality

Patient mortality was captured through the application of standardised mortality ratios (SMRs) that provided the risk of disease-specific and all-cause mortality for patients with EGPA relative to the general population.

Age- and sex-stratified general population, all-cause mortality was sourced from the Office for National Statistics (ONS) life tables (2020–2022).¹¹⁶ For each health state, the SMRs were derived from the retrospective CPRD study, and are presented in Table 40.²

Scenario analyses were conducted with varying the SMRs by +/-10% to capture the impact on the cost-effectiveness results.

Table 40: Inputs for mortality

Health state	Mean	95% CI	Source
SMR in remission (relative to general population)	■	■	CPRD ²
SMR in stable disease (relative to general population)	■	■	
SMR in relapse (relative to general population)	■	■	

Abbreviations: CI: confidence interval; CPRD: Clinical Practice Research Datalink; SE: standard error; SMR: standardised mortality ratio

B.3.3.5 Discontinuation

Discontinuation of benralizumab

The discontinuation rate of benralizumab from MANDARA was unusually low (■%) and would likely be higher in a real-world setting, as validated by clinical experts.³ In light of this, AstraZeneca explored alternative sources of discontinuation rates, such as the discontinuation rate for benralizumab in the MANDARA OLE, benralizumab in severe asthma and RWE for

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mepolizumab in EGPA. The discontinuation rates from these sources ranged from 1% to 11.8% (Table 41). Therefore, a conservative discontinuation rate of 1% per year was chosen for the base case of the economic analysis (Table 42) and was validated by clinical experts to be reflective of UK clinical practice.³ A discontinuation rate of 9.7% per year was also explored in a scenario analysis.

Table 41: Relevant treatment discontinuation rates from alternative sources

Source	Discontinuation rate per year
Benralizumab from MANDARA DB period ¹	1%
Benralizumab from MANDARA OLE ⁸⁴	1%
Benralizumab in patients with severe asthma ¹⁰³	11.8%
Mepolizumab on EGPA dose ¹¹⁷	9.7%

Abbreviations: DB: double-blind; EGPA: eosinophilic granulomatosis with polyangiitis; OLE: open-label extension

Table 42: Inputs for benralizumab discontinuation used in the base case analysis

Parameter	Mean	SE
Probability of benralizumab discontinuation (per year)	1%	1%

Abbreviations: SE: standard error

Following discontinuation of benralizumab, patients were modelled as per the effectiveness of SoC. This approach assumed that the efficacy of benralizumab was instantly lost upon discontinuation, consistent with the previous model evaluating benralizumab for severe asthma (TA565).¹⁰³ Once patients discontinued benralizumab, they were no longer eligible to reinitiate treatment at any subsequent timepoint.

Discontinuation of OCS (OCS sub-model)

In line with prescription data analysis from CPRD, 86.2% of patients entered the model receiving concomitant OCS.⁴ Treatment with benralizumab allowed patients to taper or discontinue OCS, in line with MANDARA. As described above, OCS dose reduction is a key treatment goal in EGPA, and the OCS sub-model allowed to capture the long-term health benefits and cost savings associated with the OCS-sparing benefit from benralizumab.

The inputs related to the discontinuation of OCS are presented in Table 43. Although an endpoint of MANDARA was the percentage reduction in the mean daily dose of OCS during Weeks 48 to 52 compared to baseline, time-to-OCS discontinuation was not measured. Therefore, the rate of OCS discontinuation was instead estimated by analysing data on OCS dose, which was recorded during MANDARA. For this analysis, discontinuation was assumed to be defined as a patient with an OCS dose of zero for the last 28 days of trial participation (to include patients lost to follow up). The time attributed to discontinuation was taken as the start of the interval in the contiguous stretch leading up to the end of the patient's trial participation in which the OCS dose was zero. The derived probability of OCS discontinuation from this approach 41.4% was consistent with the pre-defined percentage reduction endpoint of the trial, which was reported as 41.4% for patients receiving benralizumab.⁸³

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Given that the damage from chronic OCS doses is thought to be irreversible, once patients discontinued OCS, their risk of developing chronic and acute OCS-related comorbidities no longer increased, i.e. the risk plateaued.

As with the discontinuation of benralizumab, once patients discontinued OCS, they were no longer eligible to restart OCS. Given that guideline-directed management of EGPA is primarily based on chronic high-dose OCS, it was assumed that for SoC, ██████ were able to achieve discontinuation of OCS, as validated by clinical experts.³

Table 43: Inputs for OCS discontinuation

Parameter	Mean	SE	Source
Probability of OCS discontinuation with benralizumab (per year)	████	████	MANDARA ¹
Probability of OCS discontinuation with SoC (per year)	████	████	Assumption

Abbreviations: OCS: oral corticosteroid; SE: standard error

B.3.3.6 Adverse events

Benralizumab-related AEs were not included in the cost-effectiveness analysis given the low incidence of serious AEs observed in MANDARA,¹ and hence the minimal expected impact of AEs on patient HRQoL and NHS costs. This approach was aligned with the previous evaluation of benralizumab for severe eosinophilic asthma.¹⁰³ The safety profile of benralizumab at the higher EGPA dose in MANDARA was aligned with what is observed in severe asthma.¹⁰³

OCS-related AEs (OCS sub-model)¹⁰²

As outlined in Section B.3.2.2, the impact of acute events and chronic comorbidities caused by OCS were modelled, capturing the impacts on cost and HRQoL. The risk of developing chronic disease (modelled using prevalence) and experiencing acute events (modelled using incidence) were characterised through Cox proportional hazard regression models adjusted for cumulative OCS dose, with higher doses increasing the risk of developing disease or experiencing an acute event. The model used the mean daily dose of OCS stratified by EGPA-related health state to reflect the increased need for higher doses of OCS in the relapse and stable disease health states (compared to remission). The mean daily dose for patients residing in EGPA-related health states is presented in Table 44.

For each cycle patients resided in an EGPA-related health state, they accumulated 28 times the mean daily dose attributed to that health state, assuming the daily dose remained constant over the course of one cycle. A weighted mean dose for the entire cohort was then derived to inform the risk of developing chronic disease and acute events. Average daily doses of OCS by health state were derived from CPRD data, reflective of UK clinical practice.²

Table 44: Inputs for OCS dose for each health state

Health state	Mean (mg/day)	SE (log)	Source
Remission	████	████	CPRD ²

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Stable disease	■	■	
Relapse	■	■	

Abbreviations: OCS: oral corticosteroid; SE: standard error

Chronic disease development

Cox proportional hazard regression models were used to determine the risk of developing chronic disease as a function of cumulative OCS dose.¹⁰² To calculate the risk of comorbidity development based on OCS use, the regression model included:

- Baseline event rates, assumed to be representative of the risk of comorbidity development for patients in the general population with no prior OCS dose (Table 45)
- Coefficients representative of a one-gram increase in cumulative OCS dose, exponentiated to determine hazard ratios (HRs) which represent the increased risk of comorbidity development per gram of cumulative OCS dose (Table 46)

A risk equation was applied, with the AE event risk defined as 1 minus the exponential to the power of the baseline risk, multiplied by an exponent of the additional risk per gram to the power of the cumulative dosage in grams and the value of OCS-sparing in avoiding events accumulated over time, dependent on the extent that the patient's cumulative exposure to OCS was reduced. The value of OCS-sparing in avoiding events accumulated over time, dependent on the extent that the patient's cumulative exposure to OCS was reduced.¹⁰²

The baseline event rates were sourced from Gibson et al.,¹⁰² and were derived from the Cox proportional hazard models developed by the Observational and Pragmatic Research Institute (OPRI) which evaluated the chronic disease onset associated with OCS use based on the Optimum Patient Care Research Database (OPCRD) and the CPRD database.^{32, 110} The OPRI study investigated the impact of OCS exposure on disease onset, burden and healthcare resource use over a minimum 2-year timescale in a broad, real-world, UK patient population which consisted of patients diagnosed with conditions where OCS may be prescribed. The morbidity rates from this study are therefore considered to be generalisable to EGPA patients in UK clinical practice.

As patients resided in EGPA health states, the weighted average cumulative OCS dose was calculated across the cohort and the regression model was used to determine the mean risk of comorbidity development.

Table 45: Inputs for general population rate of chronic disease onset

Morbidity	Mean morbidity rate (per 100 patient-years)	SE (log) ^a	Source
T2DM	0.990	0.1980	Gibson et al. ¹⁰²
eCVD	1.025	0.2050	
Osteoporosis	0.369	0.0738	

Footnotes: ^aSE assumed to be 20% of the mean value.

Abbreviations: eCVD: established cardiovascular disease; SE: standard error; T2DM: type-2 diabetes mellitus

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 46: Inputs for the effects of OCS on chronic disease onset

Health state	Coefficient per 1g cumulative dose	HR (relative to general population)		Source
		Mean	SE (log)	
T2DM	0.01566642	1.016	0.0008	Gibson et al. ¹⁰²
eCVD	0.01717027	1.017	0.0006	
Osteoporosis	0.03070869	1.031	0.0018	

Abbreviations: eCVD: established cardiovascular disease; HR: hazard ratio; OCS: oral corticosteroid; SE: standard error; T2DM: type-2 diabetes mellitus

Chronic disease progression

Once OCS-related chronic disease had developed, subsequent chronic disease progression in the form of a multimorbidity was modelled to account for the increased risk of multimorbidity with continued OCS use observed in the broad population of OCS users.^{118, 119} The inputs related to chronic disease progression are presented in Table 47. All inputs were HRs for the development of an additional morbidity relative to the morbidity already being experienced; for example, the mean HR for the development of T2DM in a patient who already has eCVD was 1.170.¹¹⁸ The HRs were used to further adjust the Cox proportional hazard regression models.

The relationship between T2DM and eCVD is well discussed in the literature, with T2DM being a significant risk factor for the development of eCVD, and eCVD being the most prevalent cause of morbidity and mortality in patients with T2DM,¹²⁰⁻¹²² the inputs for these health states were sourced from studies by the QResearch group and aligned with those used in the published study from Gibson et al.^{102, 118, 119}

Table 47: Inputs for chronic disease progression

'Additional' morbidity	Relative health state	HR		Source
		Mean	SE (log)	
T2DM	eCVD	1.170 ^a	0.0085 ^b	Gibson et al. ¹⁰²
	Osteoporosis	■	■	
	eCVD and osteoporosis	■	■	
eCVD	T2DM	2.626 ^a	0.1047	
	Osteoporosis	1.300	0.0294 ^c	
	T2DM and osteoporosis	■	■	
Osteoporosis	T2DM	1.370	0.1072 ^c	
	eCVD	1.062	0.1013 ^c	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

	T2DM and eCVD	■	■	

Footnotes: ^aHR derived as the weighted average of log(HR) by reported distribution of sex.

^bSE derived using the formula $\sqrt{\frac{\sum n(\ln HR - \ln \overline{HR})^2}{\sum n - 1}}$

^cSE derived from the 95% CI around the mean using the formula $\frac{95\% CI_{upper} - 95\% CI_{lower}}{2(z_{1-\frac{\alpha}{2}})}$

Abbreviations: CI: confidence interval; eCVD: established cardiovascular disease; HR: hazard ratio; OPRI: Observational and Pragmatic Research Institute Pte. Ltd.; SE: standard error; T2DM: type-2 diabetes mellitus

Acute events

As with chronic disease onset, Cox proportional hazard regression models were used to determine the risk of developing acute events as a function of cumulative OCS dose. The mean cumulative OCS dose was used to inform the regression model and determine the risk across the entire cohort.

The inputs for the general population rate of experiencing acute events are presented in Table 48. As with the chronic disease, these event rates were derived from the Cox proportional hazard models developed by the OPRI group.¹⁰² Acute events were modelled as acute events, and as a pragmatic approach, the effects lasted the length of the cycle. A one-off cost (Section B.3.5) and utility decrement (Section B.3.4) associated with each acute event were applied in the cycle of incidence, with no further effects on OCS-related disease progression thereafter.

Table 48: Inputs for general population rate of acute event onset

Event	Mean event rate (per 100 patient-years)	SE (log) ^a	Source
Adrenal insufficiency	0.011	0.0022	Gibson et al. ¹⁰²
Cataract	0.876	0.1752	
Glaucoma	0.238	0.0476	
Peptic ulcer	0.133	0.0266	
Pneumonia	0.554	0.1108	
Renal impairment	2.359	0.4718	

Footnotes: ^aSE assumed to be 20% of the mean value

Abbreviations: OPRI: Observational and Pragmatic Research Institute; SE: standard error

Table 49: Inputs for the effects of OCS use on acute event onset

Acute event	Coefficient per 1g cumulative dose	HR (relative to general population)		Source
		Mean	SE ^a (log)	
Adrenal insufficiency ^b	NR	■ ^b	■	Gibson et al. ¹⁰²
Cataract	0.02455678	1.025	0.0009	
Glaucoma	0.01845687	1.019	0.0010	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Peptic ulcer	0.01522169	1.015	0.0013	
Pneumonia	0.02034317	1.021	0.0009	
Renal impairment	0.01853581	1.019	0.0009	

Footnotes: ^aSE derived from the 95% CI around the mean using the formula $\frac{95\% CI_{upper} - 95\% CI_{lower}}{2(z_{1-\frac{\alpha}{2}})}$

^bIncidence derived from targeted literature search, in absence of data reported from Gibson et al. publication

Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reported; OCS: oral corticosteroid; OPRI: Observational and Pragmatic Research Institute; SE: standard error

B.3.4 Measurement and valuation of health effects

As discussed in Section B.1.3.1, EGPA is characterised by severe, multi-system manifestations and organ damage, which contribute to a considerable negative impact on many aspects of patients' quality of life. Patients experience multiple disruptions to daily living including severe fatigue, functional impairment, sleep disruption, emotional distress, anxiety and a reduced ability to work and engage in social activities. Additionally, current SoC (OCS and IS) have limited effectiveness with high relapse rates and short times to relapse. This leaves patients cycling through the EGPA health states, causing patients to feel low, scared, frustrated and anxious, exacerbating negative feelings about future outcomes. Furthermore, OCS are associated with severe, chronic and acute AEs, compounding the impact of EGPA on HRQoL. Therefore, utilities dependent on each health state and disutilities associated with OCS-related AEs were modelled to capture the potential impact of EGPA and OCS use on HRQoL.

B.3.4.1 Health-related quality-of-life data from clinical trials

The MANDARA trial collected HRQoL data using the SF-36 questionnaire. SF-36 is an instrument used for assessing general health and QoL, with questions on eight domains of health, including physical and social functioning.¹²³ The HRQoL analysis was based on data pooled from the mepolizumab and benralizumab arms, as this increased the sample size for the analysis, and the HRQoL data were stratified by disease status, independent of treatment arm.

B.3.4.2 Mapping

The SF-36 data collected in MANDARA were mapped to EQ-5D-3L (henceforth referred to as just "EQ-5D"), to abide to the NICE reference case, which advocates for EQ-5D as the preferred method for valuing HRQoL. As there is no preferred mapping algorithm in the NICE reference case, two published methods were explored: Ara and Brazier, 2008 and Rowen et al., 2009.^{124, 125}

The mapping algorithm developed by Rowen et al.¹²⁵ was used for the analysis, due to a larger sample size used to derive the mapping algorithm and the higher R². Rowen et al. also concluded that when measuring goodness-of-fit statistics, their model performed better than the Ara and Brazier model. The Rowen model mapped SF-36 scores to EQ-5D scores, and utility values were generated using the UK value set derived by Dolan et al.¹²⁶ Once EQ-5D index scores were generated, health state utility values were generated based on a "crude" mean of index scores attributed to the time-updated health states observed in the MANDARA trial. In this

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

instance “crude” refers to averaging across all observations, for which some patients had multiple observations.

MANDARA started recruitment in 2019. The understanding of EGPA has subsequently evolved as explained in B.3.2.2, and it was important to reflect four relevant health states in the economic analysis. However, quality of life data in MANDARA were only collected for the remission, stable disease and relapse health states. To address this limitation, IPD have since been retrospectively analysed to generate the utility values for the non-refractory and refractory health states. Table 50 presents the results of SF-36 from MANDARA mapped to EQ-5D.

However, the quality of life results from MANDARA were not consistent with the insights gathered from patient and clinical expert interviews for the two reasons outlined below.^{3, 70} The potential reasons why this might be the case are presented in Table 51.

1. Minimal utility difference between remission and relapse
 - a. Clinical experts and patients consistently highlighted how HRQoL is significantly better in remission compared to relapse – based on the considerably alleviated symptom burden and lower doses of medication (OCS dose in particular)
2. Refractory not being the health state with the lowest utility
 - a. Clinical experts and patients mention the severe symptoms limiting their daily activities and social life combined with the psychological impact of not having achieved remission for 6 months and the despair, anxiety and frustration they experience in the refractory health state result in a significant negative impact on their wellbeing

In summary, the mapped utility data from MANDARA did not accurately capture the patient experience of living with EGPA, as validated by clinical experts.³ Therefore, the trial utility data were not used in the economic model, and alternative approaches were investigated further (Section B.3.4.4).

Table 50: Results of SF-36 mapped to EQ-5D

Health State	SF-36 mapped to EQ-5D (Original data available from MANDARA)	SF-36 mapped to EQ-5D (IPD retrospectively analysed from MANDARA)
Remission	■	■
Stable disease	■	■
Non-refractory	■	■
Refractory	■	■
Relapse	■	■

Abbreviations: IPD: individual patient data; SF-36: Short form 36-item health survey

Table 51: Rationale for SF-36 limitations

Limitation	Rationale
SF-36 does not capture the full symptom burden in EGPA	- Clinical experts noted concerns about SF-36 not capturing the patients' experience of living with EGPA, and challenged the suitability of SF-36 for measuring QoL in EGPA³ - A recent SLR on patient-reported outcomes in AAV reported no meaningful relationship between SF-36 and BVAS¹²⁷ - Furthermore, it has been shown that the SF-36 PCS may not accurately measure the physical health status of patients.¹²⁸ The PCS domain includes physical functioning (impact on daily activities), impact on work because of impaired physical functioning and general health. This limitation is of particular importance in EGPA as the disease has a significant impact on the physical health of patients due to multi-system manifestations, damage to multiple organ systems and substantial fatigue; this reduces patients' ability to work and conduct daily activities. Therefore, the HRQoL impact of EGPA may be under-estimated by SF-36 - The OMERACT Vasculitis Working Group has consistently highlighted concern that the SF-36 may not capture all important aspects of the EGPA¹²⁹
Value lost mapping from SF-36 to EQ-5D	- It is common occurrence for HRQoL data to lose predictive validity and any additional sensitivity when mapped to another preference-based measure¹²⁵ - This may have caused the utility values for each health state to converge, losing sensitivity to the distinct HRQoL impacts of each health state

Abbreviations: AAV: ANCA-associated vasculitis; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; EQ-5D: EuroQol 5-Dimensions; HRQoL: health-related quality of life; OCS: oral corticosteroids; OMERACT: Outcome Measures in Rheumatology; PCS: physical component summary; HRQoL: health-related quality of life; SF-36: Short form 36-item health survey; SLR: systematic literature review

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.4.3 Health-related quality-of-life studies

As described in Section B.3.1, an SLR was conducted in July 2023 to identify studies HRQoL data for patients with EGPA, with an update conducted in 2024. Full details of the SLR search strategy, methodology and results are presented in Appendix H.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

As described across Sections B.3.4.1 to B.3.4.3, there were limitations with HRQoL from MANDARA, and the SLR [REDACTED] utility data. In light of this, extensive work was undertaken to address the limitations of the trial utility data and generate robust evidence to accurately represent QoL in an EGPA-specific population – which was challenging, given the rarity of the disease. There were two studies which were conducted to address this data limitation; the Adelphi Real World Disease Specific Programme (thereafter referred to as Adelphi DSP) and a UK-specific vignette study.^{39, 74}

Both RWE studies provided HRQoL data which were granular enough to inform HRQoL for all the four health states considered in this submission. Each study had its own merit:

- Adelphi DSP: 177 patients (9 from the UK) completed the EQ-5D questionnaire in the study, which was a significant source of data, given the rarity of EGPA
- UK-specific vignette study: UK-specific HRQoL data was collected, thus providing an opportunity to leverage data most reflective of UK EGPA patients

An overview of each study is provided in Table 52. The health state descriptions derived from interviews, as part of conducting the vignette study are presented in Appendix O. The approach of obtaining alternative HRQoL values including vignettes, to help inform decision making, is consistent with the Committee recommendation in TA981.¹³⁰

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 52: Adelphi DSP and vignette study methodology

Workstream	Description of study and methodology
Adelphi DSP study ⁷⁴	- The study was a cross-sectional physician and patient survey conducted in France, Germany, Italy, Spain, UK and US between July to December 2023 - Patients' disease severity was based on physician's definition and patients completed EQ-5D-5L questionnaires - The utility scores generated from EQ-5D-5L were cross walked to EQ-5D-3L using the UK tariff, making results suitable for UK decision making
Vignette study ³⁹	- Vignette descriptions were developed based on findings from a literature review, analysis of patient-level data from MANDARA, and interviews with 8 patients with EGPA, 4 clinical experts well-versed in treating patients with EGPA and 1 HRQoL expert who is experienced with EGPA. - Valuation of vignettes was conducted with 300 members of the general public and 21 patients with EGPA 21 patients with EGPA completing the valuation of the health states are a significant number of patients, given the rarity of the disease (70 patients in the benralizumab arm of the MANDARA trial) - Participants completed EQ-5D-5L questionnaires, and the utility scores generated from EQ-5D-5L were cross-walked to EQ-5D-3L using the UK tariff - The vignettes were developed and conducted in line with DSU guidance¹³¹

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; DSP: disease specific programme; DSU: Decision Support Unit; HRQoL: health-related quality of life; UK: United Kingdom; US: United States

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Results from the Adelphi DSP (general population and patient valuation) and vignette study are presented in Table 53.

Table 53: Adelphi DSP and vignette study results

Health State	Adelphi DSP	Vignette	
		General population valuation	Patient valuation
Remission	■	■	■
Non-refractory	■	■	■
Refractory	■	■	■
Relapse	■	■	■

Abbreviations: DSP: disease specific programme

The insights and interpretation from the Adelphi DSP and vignette study are presented in Table 54.

Table 54: Interpretation of Adelphi DSP and vignette study results

Observation	Applicable to which study?	Implication
Clear differentiation in utility values between each health state	Both	Supports the fact that there are four distinct relevant health states
Significant difference between remission and relapse utility	Both	In line with the insights from patient and clinical expert interviews
Refractory health state has the lowest utility	Both	In line with the insights from patient and clinical expert interviews
Refractory health state utility valuation from vignette is low	Vignette study	Refractory health state is clearly a poorly valued health state, and distinct from other health states

Abbreviations: DSP: disease specific programme

Although the utility value for the refractory health state was rated consistently by patients and the general population, the value was unusually low considering utility values observed for the other health states as well as other diseases. Considering the sensitivity of this parameter, a more conservative set of assumptions was chosen, based on Adelphi DSP.

Adelphi DSP was deemed the most appropriate source to inform HRQoL in the base case for the below reasons:

- It provided utility for all four health states, in the form of EQ-5D, NICE's preferred measure of HRQoL
- 177 patients completed the EQ-5D questionnaire, which is a significant source of data, given the rarity of EGPA – this was the biggest sample size to inform HRQoL [compared to MANDARA (N=140) and patient valuation of the vignette study (N=21)]
- The utility values were mapped using a UK tariff – thereby making the results suitable for UK decision making

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

- Patients' disease severity was based on physician's definition – thereby simulating what will be the case in UK clinical practice
- Adelphi DSP provided an objective and impartial source of data, where clinical and subjective variables were captured from both a physician and patient perspective
- Standard deviations around the mean utility scores were low
- Adelphi DSP was the EAG and Committee's preferred assumption in TA958 and was considered the most appropriate source to inform QoL for decision making¹³²
- The values were validated by clinical experts as being reflective of the HRQoL of UK EGPA patients³

A scenario analysis with utility values from the general population and patient valuation is presented in Section B.3.10.3.

B.3.4.5 Adverse reactions

As explained in Section B.3.3.6, benralizumab-related AEs were not included in the cost-effectiveness analysis given the low incidence of serious AEs observed in MANDARA,¹ and hence the minimal expected impact of AEs on patient HRQoL and NHS costs. The safety profile of benralizumab at the higher EGPA dose in MANDARA was aligned with what is observed in severe asthma.¹⁰³

The analysis captured the impact of OCS-related comorbidities and acute events on HRQoL, through the application of utility decrements. For each cycle that patients resided in a chronic disease health state, they accrued the relevant utility decrement which was applied additively to the health state utilities for EGPA. As acute events occurred only in the cycle of incidence, a one-off utility decrement was applied in the same cycle. Chronic disease utility decrements were input into the cost-effectiveness model as annualised utility decrements and were scaled to 28-day decrements to match the cycle length of the model. Where patients experience multiple comorbid AEs, a multiplicative approach was taken to combining the associated disutilities.

The utility decrements applied in the model are presented in Table 55. In the absence of HRQoL data from MANDARA stratified by OCS-related morbidity or acute event, all utility decrements were sourced from a catalogue of EQ-5D index scores based on UK preference weights, derived from a general population sample of 79,522 patients, ensuring incorporation of the preferences of the UK general public.¹³³

Table 55: Utility decrements for chronic OCS-related comorbidities and acute events

Morbidity or event	Mean	SE	Source
Chronic disease			
T2DM	-0.062	0.0038	Sullivan et al. 2011 ¹³³
eCVD ^a	-0.087	0.0155	
Osteoporosis	-0.042	0.0063	
Acute events			
Adrenal insufficiency ^b	■	■	Assumption
Cataract	-0.027	0.0060	Sullivan et al. 2011 ¹³³

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Glaucoma	-0.028	0.0063	
Peptic ulcer	-0.055	0.0140	
Pneumonia	-0.079	0.0420	
Renal impairment	-0.096	0.0115	

Footnotes: ^a Mean derived as the average of utility decrements for MI (-0.056), stroke (-0.101) and HF (-0.103). SE derived as the standard deviation of the utility decrements for MI, stroke and HF divided by the square root of three. ^bIn absence of data reported from Gibson et al. publication, conservative assumption of no disutility adopted
Abbreviations: eCVD: established cardiovascular disease; HF: heart failure; MI: myocardial infarction; OCS: oral corticosteroid; SE: standard error; T2DM: type-2 diabetes mellitus

B.3.4.6 Summary of utility data used in the cost-effectiveness analysis

A summary of the utility values used in the model is provided in Table 56.

Table 56: Summary of utility values for the cost-effectiveness analysis

State	Utility value	SE	Reference in submission (section and page number)	Rationale
Health states				
Remission	0.766	0.0168	Section B.3.4.4, page 98	See Section B.3.4.4
Non-refractory	0.746	0.0185		
Refractory	0.500	0.0704		
Relapse	0.638	0.0404		
OCS-related chronic disease and acute events				
T2DM	-0.062	0.0038	Section B.3.4.5, page 101	Common and representative chronic OCS-related comorbidities and acute events. Based on Sullivan et al. 2011 ¹³³ in the absence of data from MANDARA
eCVD ^a	-0.087	0.0155		
Osteoporosis	-0.042	0.0063		
Adrenal insufficiency ^b	■	■		
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		

Footnotes: ^a Mean derived as the average of utility decrements for MI (-0.056), stroke (-0.101) and HF (-0.103). SE derived as the standard deviation of the utility decrements for MI, stroke and HF divided by the square root of three. ^bIn absence of data reported from Gibson et al. publication, conservative assumption of no disutility adopted
Abbreviations: eCVD: established cardiovascular disease; OCS: oral corticosteroids; SE: standard error; T2DM: type-2 diabetes mellitus

B.3.4.7 Age-based utility decrement

Age-adjusted utility values were implemented in the model to account for the expected decrease in HRQoL over time associated with aging. The utility estimates for each model cycle were adjusted based on the difference between patients' mean age during the current cycle and the mean age at baseline (see Section B.3.3.1 for starting age). The age-adjusted utilities were implemented using mean EQ-5D-3L values by age, estimated from the latest available wave of the Health Survey for England (HSE) that included the EQ-5D-3L.¹³⁴ A proportional age

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

adjustment factor for each year was calculated based on the mean utility at the measured age (e.g., the starting age from the CPRD cohort is [REDACTED] years) and the corresponding age-adjusted utility in every year. The age adjustment was applied to the mean utility in a multiplicative fashion in each cycle of the model.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

As described in Section B.3.1, a *de novo* SLR was conducted in June 2023, and updated in August 2024 to identify HCRU evidence in EGPA. [REDACTED] studies were identified, which were relevant to this submission.

All costs presented throughout this section have been inflated to 2024 costs, using a standard inflation index (National Health Service Cost Inflation Index).¹⁰⁵

B.3.5.1 Intervention and comparators’ costs and resource use

Drug acquisition costs

Intervention: benralizumab

Patients in receipt of benralizumab in the economic model incurred costs of benralizumab and costs associated with the background use of SoC. The acquisition cost of benralizumab is presented in Table 57. Once patients discontinued treatment with benralizumab, they ceased to accrue any treatment-related costs of benralizumab and were subjected to the treatment costs of SoC alone.

Table 57: Acquisition costs for benralizumab

Treatment	Dosing schedule	Unit		Per model cycle		Source
		Dose	Cost	Units	Cost	
Benralizumab	30 mg Q4W	30 mg	List price: £1,955 PAS price: £[REDACTED]	1	List price: £1,955 PAS price: £[REDACTED]	BNF ¹³

Abbreviations: BNF: British National Formulary; Q4W: every 4 weeks

Comparator: SoC

As discussed in Section B.1.3.3, SoC for patients with EGPA consists of OCS and IS. Therefore, the comparator arm costs consist of a weighted average of OCS (prednisolone) and IS agents (azathioprine, mycophenolate mofetil and methotrexate). OCS treatment can be discontinued, however, IS therapy is generally not discontinued, and this was reflected in the way these treatments were modelled. The cost per cycle of SoC treatment was dependent on the percentage of EGPA patients receiving OCS, which varied each model cycle as patients discontinued the treatment, and a fixed cost of IS, which was taken as a weighted average of the costs of the three most common therapies.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

The acquisition costs associated with SoC are presented in Table 58. Prednisolone was chosen to represent all OCS used in EGPA, as discussed in Section B.3.2.3, which has its price per pack converted to a cost per mg, to apply to the daily dose of OCS used in the model. It was assumed that the daily dose for each health state was held constant for the duration of a model time horizon. The IS weighted average was comprised of azathioprine, mycophenolate mofetil and methotrexate. There was not an option to discontinue IS treatment in the model, so IS costs are fixed over time. The distribution for each OCS and IS therapy was informed by CPRD and is presented in Table 58. Costs were derived from the electronic market information tool (eMIT), which provides information about prices for generic drugs and pharmaceutical products in the UK.¹⁰⁴

Drug administration costs

Benralizumab is a self-administered pre-filled pen, therefore no administration-related costs were modelled. Similarly, OCS and relevant IS are administered orally, incurring no administration costs.

B.3.5.2 Health-state unit costs and resource use

As detailed in Section B.1.3.1, EGPA is associated with a high-cost burden to the NHS due to the multiple organ systems affected, the lengthy period of time taken to an official diagnosis (reported as 7.1–11.8 years.^{38, 40}) and, therefore, the multidisciplinary approach taken to treatment. This includes visits to HCPs of varied disciplines, as well as hospital visits for disease management and monitoring. Therefore, in the cost-effectiveness model, for each cycle that patients resided in a health state, they incurred the relevant disease management and monitoring costs. Health state costs were input as annual costs and were scaled to 28-day costs to match the cycle length of the model and were inflated to net present values using inflation factors collated from historical versions of PSSRU.¹⁰⁶

The frequency of healthcare resource use were derived from CPRD (Table 59), in which a retrospective analysis of HCRU in EGPA based on patient records and stratified by health states was conducted.² The study considered patients in the CPRD database with their first EGPA diagnosis code between 1 January 2006 and 28 February 2019, with at least 12 months of pre-diagnosis registration.

Unit costs were sourced from NHS reference costs 2021–2022¹⁰⁵ and PSSRU 2023¹⁰⁶ and are presented in Table 60. The frequency of resource use per year was multiplied by the respective unit costs to derive health-state specific HCRU costs per year for the model.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 58: Acquisition costs for SoC

Treatment	Distribution within regimen	Unit			Model cycle			Source
		Tablets	Dose/ tablet	Cost	Dose ^a	Cost	SE	
OCS								
Prednisolone	86.2%	28	5mg	£0.41	1 mg ²	£0.00293	£0.000001	eMIT ¹⁰⁴
IS								
Azathioprine	32.5%	56	50mg	£1.20	████ mg/day ²	£0.00043	£0.000000	eMIT ¹⁰⁴
Mycophenolate mofetil	14.8%	50	500mg	£6.55	████ mg/day ²	£0.00026	£0.000000	eMIT ¹⁰⁴
Methotrexate	17.5%	100	2.5mg	£3.18	████ mg/day ²	£0.01271	£0.000009	eMIT ¹⁰⁴

Footnote: ^a This is an example dose for OCS, the exact dose varies by health state

Abbreviations: eMIT: electronic market information tool; SE: standard error

Table 59: Frequency of healthcare resource use, by health state, per patient per year for disease management

Resource	Remission	Stable disease	Relapse	Source
	Mean	Mean	Mean	
GP consultations	█	█	█	CPRD ²
Nurse consultations	█	█	█	
Outpatient visits	█	█	█	
ED visits	█	█	█	
Hospitalisations	█	█	█	
Critical care visits	█	█	█	

Abbreviations: CPRD: Clinical Practice Research Datalink; ED: emergency department; GP: general practitioner

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 60: Unit costs for disease management

Resource	Unit costs		
	Mean	Description	Source
GP consultations	£49.00	Per surgery consultation lasting 10 minutes, with direct care staff costs, with qualification costs	PSSRU 2023 ¹⁰⁶
Nurse consultations	£8.83 ^a	Per consultation lasting 10 minutes, with qualification costs	
Outpatient visits	£188.08	Total outpatient attendance, service code 340: respiratory medicine service, total cost, consultant led	National Cost Collection 2022–2023 ¹⁰⁵
ED visits	£262.68	Weighted average of total HRG, currency code VB01Z to VB11Z	
Hospitalisations	£1,217.53	Weighted average of total HRG, currency code DZ15M to DZ15R	
Critical care visits	£2,424.72	Weighted average of critical care, currency code XC01Z to XC07Z	

Footnotes: ^aDerived from cost of £53 per hour. Assumed consultation lasts equivalent time as with GP

Abbreviations: ED: emergency department; GP: general practitioner; HRG: Healthcare Resource Group; PSSRU: Personal Social Services Research Unit

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.5.3 Adverse reaction unit costs and resource use

As explained in Section B.3.3.6, AEs for benralizumab were not modelled. The model captured the costs of morbidities and acute events associated with chronic OCS use. As acute events occurred only in the cycle of incidence, a one-off event cost was applied in the same cycle. Chronic disease health state costs were input as annual costs and were scaled to 28-day costs to match the cycle length of the model. The costs utilised in the model for chronic OCS-related comorbidities are presented in Table 61 and aligns with the approach of Gibson et al. 2024.¹⁰²

Table 61: Costs for chronic OCS-related comorbidities and acute events

Resource	Mean	SE	Source
Chronic disease			
T2DM	£3,160.71	£39.532	Wang et al. ¹³⁵
eCVD	£3,416.93	£673.795	Danese et al. ¹³⁶
Osteoporosis	£3,199.91	£639.982	National Cost Collection 2022-23 ¹⁰⁵
Acute events			
Adrenal insufficiency	£2,416.11 ^a	£483.222	Chauhan et al. ¹³⁷
Cataract	£967.69	£193.537	National Cost Collection 2022-23 ¹⁰⁵
Glaucoma	£844.32	£168.863	
Peptic ulcer	£825.18	£165.035	Pritchard et al. ¹³⁸
Pneumonia	£4,486.56	£14.742	Campling et al. ¹³⁹
Renal impairment	£2,631.93 ^b	£526.385	National Cost Collection 2022-23 ¹⁰⁵

Abbreviations: eCVD: established cardiovascular disease; OCS: oral corticosteroid; SE: standard error; T2DM: type-2 diabetes mellitus.

Footnotes: ^aApplied as a one-off cost in cycle of incidence; ^bAssumed as cost of acute kidney injury

B.3.6 Severity

Hypereosinophilia in patients with EGPA leads to a wide variety of serious disease manifestations, such as asthma, cardiac issues, GI conditions and ENT manifestations, resulting in long-term organ damage and causing significant morbidity and mortality.¹⁸⁻²⁰ EGPA symptoms, such as neuropathy, pain, fatigue and weight loss and the associated accumulated organ damage negatively impact patient HRQoL in the long-term, leading to mental health impacts, reduced physical activity and impaired ability to work.^{22, 23}

Despite the established severity of EGPA, this submission would not be eligible for the NICE severity modifier based on a QALY shortfall analysis (Table 62).

Table 62: Summary of QALY shortfall analysis

	QALY shortfall
Absolute	■
Proportional	■

Abbreviations: QALY: quality-adjusted life year

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.7 Managed access proposal

AstraZeneca does not wish to present a managed access proposal for benralizumab in this indication.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of inputs utilised in the deterministic base case is presented in Table 63. Measurements of uncertainty are provided in Appendix P.

Table 63: Summary of base case inputs

Variable	Value	Reference to section in submission
Baseline demographics		
Age (years)	████	Section B.3.3.1
Percentage male	████	
Baseline comorbidities		
Proportion with T2DM without eCVD and osteoporosis	████	Section B.3.3.1
Proportion with eCVD without T2DM and osteoporosis	████	
Proportion with osteoporosis without T2DM and eCVD	████	
Proportion with T2DM and eCVD without osteoporosis	████	
Proportion with T2DM and osteoporosis without eCVD	████	
Proportion with eCVD and osteoporosis without T2DM	████	
Proportion with T2DM and eCVD and osteoporosis	████	
Transition probabilities – Benralizumab pre-response		
Remission -> Remission	████	Section B.3.3.2
Remission Relapse-free	████	
Remission -> Relapse	████	
Relapse-free -> Remission	████	
Relapse-free -> Relapse-free	████	
Relapse-free -> Relapse	████	
Relapse -> Remission	████	
Relapse -> Relapse-free	████	
Relapse -> Relapse	████	
Transition probabilities – Benralizumab responders		
Remission -> Remission	████	Section B.3.3.2
Remission Relapse-free	████	
Remission -> Relapse	████	
Relapse-free -> Remission	████	
Relapse-free -> Relapse-free	████	
Relapse-free -> Relapse	████	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Relapse -> Remission	████	
Relapse -> Relapse-free	████	
Relapse -> Relapse	████	
ITC		
RR for rate of relapse with benralizumab (relative to SoC)	██	Section B.3.3.2
OR for odds of remission with benralizumab (relative to SoC)	██	
Transition probabilities – SoC		
Remission -> Remission	████	Section B.3.3.2
Remission Relapse-free	████	
Remission -> Relapse	████	
Relapse-free -> Remission	████	
Relapse-free -> Relapse-free	████	
Relapse-free -> Relapse	████	
Relapse -> Remission	████	
Relapse -> Relapse-free	████	
Relapse -> Relapse	████	
Refractory disease		
Proportion of patients attributed to refractory disease: benralizumab (Baseline)	██	Section B.3.2.2
Proportion of patients attributed to refractory disease: benralizumab (End of time period)	██	
Proportion of patients attributed to refractory disease: SoC (Baseline)	██	
Proportion of patients attributed to refractory disease: SoC (End of time period)	██	
Response		
Time of response assessment (weeks)	52	Section B.3.3.2
Probability of achieving response upon assessment	████	
All-cause mortality		
SMR for patients in remission (relative to general population)	██	Section B.3.3.3
SMR for patients in relapse-free (relative to general population)	██	
SMR for patients in relapse (relative to general population)	██	
Benralizumab attrition		
Probability of benralizumab discontinuation (per year)	█	Section B.3.3.5
OCS discontinuation		
Probability of OCS discontinuation: benralizumab (per year)	████	Section B.3.3.5
Probability of OCS discontinuation: SoC (per year)	████	
OCS dosing		
Dose of OCS for patients in remission (mg/day)	██	Section B.3.3.6
Dose of OCS for patients in relapse-free (mg/day)	████	
Dose of OCS for patients in relapse (mg/day)	████	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

General population chronic disease		
Rate of T2DM in the general population (per 100 patient-years)	0.990	Section B.3.3.6
Rate of eCVD in the general population (per 100 patient-years)	1.025	
Rate of osteoporosis in the general population (per 100 patient-years)	0.369	
Cumulative OCS effects on chronic disease		
HR for rate of T2DM (relative to general population; per 1g of cumulative OCS dose)	1.016	Section B.3.3.6
HR for rate of eCVD (relative to general population; per 1g of cumulative OCS dose)	1.017	
HR for rate of osteoporosis (relative to general population; per 1g of cumulative OCS dose)	1.031	
Chronic disease progression		
HR for rate of T2DM (relative to eCVD)	1.170	Section B.3.3.6
HR for rate of T2DM (relative to osteoporosis)	■	
HR for rate of eCVD (relative to T2DM)	2.626	
HR for rate of eCVD (relative to osteoporosis)	1.300	
HR for rate of osteoporosis (relative to T2DM)	1.370	
HR for rate of osteoporosis (relative to eCVD)	1.062	
HR for rate of T2DM (relative to eCVD and osteoporosis)	■	
HR for rate of eCVD (relative to T2DM and osteoporosis)	■	
HR for rate of osteoporosis (relative to T2DM and eCVD)	■	
General population acute events		
Rate of adrenal insufficiency in the general population (per 100 patient-years)	0.011	Section B.3.3.6
Rate of cataract in the general population (per 100 patient-years)	0.876	
Rate of glaucoma in the general population (per 100 patient-years)	0.238	
Rate of peptic ulcer in the general population (per 100 patient-years)	0.133	
Rate of pneumonia in the general population (per 100 patient-years)	0.554	
Rate of renal impairment in the general population (per 100 patient-years)	2.359	
Cumulative OCS effects on acute events		
HR for rate of adrenal insufficiency (relative to general population; per 1g of cumulative OCS dose)	■	Section B.3.3.6
HR for rate of cataract (relative to general population; per 1g of cumulative OCS dose)	1.025	
HR for rate of glaucoma (relative to general population; per 1g of cumulative OCS dose)	1.019	
HR for rate of peptic ulcer (relative to general population; per 1g of cumulative OCS dose)	1.015	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

HR for rate of pneumonia (relative to general population; per 1g of cumulative OCS dose)	1.021	
HR for rate of renal impairment (relative to general population; per 1g of cumulative OCS dose)	1.019	
Healthcare resource use		
Remission: GP consultations (per year)	■	Section B.3.5.2
Remission: Nurse consultations (per year)	■	
Remission: Outpatient visits (per year)	■	
Remission: A&E visits (per year)	■	
Remission: Hospitalisations (per year)	■	
Remission: Critical care visits (per year)	■	
Stable disease: GP consultations (per year)	■	
Stable disease: Nurse consultations (per year)	■	
Stable disease: Outpatient visits (per year)	■	
Stable disease: A&E visits (per year)	■	
Stable disease: Hospitalisations (per year)	■	
Stable disease: Critical care visits (per year)	■	
Relapse: GP consultations (per year)	■	
Relapse: Nurse consultations (per year)	■	
Relapse: Outpatient visits (per year)	■	
Relapse: A&E visits (per year)	■	
Relapse: Hospitalisations (per year)	■	
Relapse: Critical care visits (per year)	■	
Disease management costs		
GP consultation	£49.00	Section B.3.5.2
Nurse consultation	£8.83 ^b	
Outpatient visit	£188.08	
A&E visit	£262.68	
Hospitalisation	£1,217.53	
Critical care visit	£2,424.72	
Biologic drug acquisition costs		
Benralizumab (per 30mg dose)	£1,955.00	Section B.3.5.1
Benralizumab (per 30mg dose) with PAS discount	£■	
SoC drug acquisition		
Proportion of patients receiving azathioprine	32.5%	Section B.3.5.1
Proportion of patients receiving mycophenolate mofetil	14.8%	
Proportion of patients receiving methotrexate	17.5%	
Dose of azathioprine (mg/day)	■	
Dose of mycophenolate mofetil (mg/day)	■	
Dose of methotrexate (mg/day)	■	
Cost of prednisolone (per mg)	£0.00293	
Cost of azathioprine (mg/day)	£0.00043	

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Cost of mycophenolate mofetil (mg/day)	£0.00026	
Cost of methotrexate (mg/day)	£0.01271	
OCS chronic disease costs		
T2DM (per year)	£3,160.71	Section B.3.5.3
eCVD (per year)	£3,416.93	
Osteoporosis (per year)	£3,199.91	
OCS acute event costs		
Adrenal insufficiency (per event)	£2,416.11	Section B.3.5.3
Cataract (per event)	£967.69	
Glaucoma (per event)	£844.32	
Peptic ulcer (per event)	£825.18	
Pneumonia (per event)	£4,486.56	
Renal impairment (per event)	£2,631.93	
Health state utilities		
Remission	■	Section B.3.4.4
Non-refractory	■	
Refractory	■	
Relapse	■	
OCS chronic disease utility decrements		
Utility decrement for T2DM (per year)	-0.062	Section B.3.4.5
Utility decrement for eCVD (per year)	-0.087	
Utility decrement for osteoporosis (per year)	-0.042	
OCS acute events utility decrements		
Utility decrement for adrenal insufficiency (per event)	■	Section B.3.4.5
Utility decrement for cataract (per event)	-0.027	
Utility decrement for glaucoma (per event)	-0.028	
Utility decrement for peptic ulcer (per event)	-0.055	
Utility decrement for pneumonia (per event)	-0.079	
Utility decrement for renal impairment (per event)	-0.096	

Abbreviations: A&E: accident and emergency; CI: confidence interval; DSA: deterministic sensitivity analysis; eCVD: established cardiovascular disease; EGPA: eosinophilic granulomatosis with polyangiitis; GP: general practitioner; HR: hazard ratio; ITC: indirect treatment comparison; NA: not applicable; OCS: oral corticosteroid; OR: odds ratio; PSA: probabilistic sensitivity analysis; RR: rate ratio; SE: standard error; SMR: standardised mortality ratio; SoC: standard of care; T2DM: type-2 diabetes mellitus.

B.3.8.2 Assumptions

Assumptions used in the overarching economic model and the OCS-sub model are described in Table 64.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 64: Assumptions in the economic model

Assumption	Rationale	Reference to section in submission
Overarching economic model		
The effect of long-term organ damage due to EGPA was not captured in the model	Based on evidence in the literature, damage to organ systems has a significant role in the long-term morbidity of patients with EGPA, particularly cardiovascular and respiratory impairment. Given that increased organ damage (VDI) scores would be expected over the course of a year-long trial, the stability in these scores observed in the benralizumab arm of MANDARA, indicated halting of disease progression, which is a positive outcome for patients with EGPA.^{47, 83} By depleting eosinophils and inducing sustained remission, benralizumab is expected to prevent further organ damage¹ and reduce the risk of cardiac and respiratory involvement, slowing disease progression However, separating individual organ involvement and performing heterogenous analyses to feed into an individual patient-level simulation model was not deemed appropriate due to the scarcity of robust data required to inform a model with that level of complexity. Therefore, as a conservative approach, the model does not capture disease progression dependent on individual organ involvement, nor does it reflect the severity of a relapse based on a particular organ involvement	Section B.3.12
The refractory and non-refractory health states were modelled as sub-states within the stable disease health state	Due to the limited sample size in MANDARA (N=70 patients in the benralizumab arm), transition probabilities to and from the non-refractory and refractory health states from other health states could not be derived from the trial data. ¹ Given these data limitations, the refractory and non-refractory health states were modelled as sub-states within the stable disease health state.	Section B.3.2.2
The proportion of refractory patients in the SoC arm stayed constant over time	CPRD analysis showed that the proportion of refractory patients stayed constant over 5 years and clinical experts validated this assumption ³	Section B.3.3.3
The transition probabilities for the benralizumab arm, derived from a 52-week trial, stayed constant for the duration of the time horizon	The assumption of no treatment waning effect was consistent with an evaluation of benralizumab for severe eosinophilic asthma (TA565) and validated by clinical experts. ^{3,103}	Section B.3.3.2

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Transition probabilities for SoC arm to stable disease were assumed equivalent to benralizumab arm to stable disease	For the SoC arm of the model, as a conservative assumption, the probability of entering the stable disease health state was assumed equivalent to that in the benralizumab arm in the absence of comparative effectiveness evidence for such transitions from the Bucher ITC	Section B.3.3.2
Benralizumab-related AEs were not included in the model	Benralizumab-related AEs were not included in the cost-effectiveness analysis given the low incidence of serious AEs observed in MANDARA, in line with the approach in TA565. ^{1,103} In addition, benralizumab at the higher EGPA dose has a safety profile, aligned to that of benralizumab in the previous trials in asthma ¹⁰³	Section B.3.3.6
The relative efficacy of benralizumab versus SoC was informed by a Bucher ITC in the base case, based on the assumption of comparability between the MANDARA and MIRRA trials	The similarity between the MANDARA and MIRRA trials in terms of trial design, population and outcome measurements was confirmed by clinical experts. ^{1, 3, 34} Therefore, no adjustment for treatment effect modifiers was deemed necessary, and a Bucher ITC was considered most appropriate	Section B.2.9.3
No patients in SoC arm discontinued OCS	This was in line with UK clinical practice, where clinicians would not discontinue OCS if patients were only on SoC (OCS +/- IS) ³	Section B.3.3.5
Following discontinuation of OCS, the risk of developing acute and chronic OCS related AEs remained constant	This assumption was in line with the modelling approach used in the evaluation of benralizumab for severe asthma and validated by clinical experts ³	Section B.3.3.5
The use and costs of concomitant medications such as inhaled and topical steroids have not been considered in the analysis	This assumption was made in the interest of simplicity; however, this is a conservative assumption as clinical experts highlighted that benralizumab would be expected to reduce the need for nasal and topical steroids ³	Section B.3.5
OCS sub-model		
The model used a surrogate relationship between OCS and OCS-related AEs	As the MANDARA clinical trial was not powered to detect the long-term effects of OCS-sparing, a surrogate relationship between OCS dose and OCS-related AEs was informed through a large UK based RWE study. This study quantified the long-term risk of developing chronic outcomes as a function of OCS dose. The evidence from this study was leveraged into this model via the OCS sub-model to characterise the burden of patients receiving chronic OCS as a treatment for EGPA	Section B.3.2.2

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Mortality was not modelled in the OCS sub-model	Given 5 years of follow-up data were available from CPRD on all-cause mortality, the explicit mortality attributed to the OCS sub-model would likely exceed that of CPRD, which would lack face validity. ² In addition, modelling the independent mortality of the OCS sub-model would require combining all health states, which would yield 24 health states and add additional complexity	Section B.3.2.2
Cumulative OCS was modelled per health state rather than per treatment	The treatment effect of benralizumab is maintaining patients in remission and reducing the time in relapse. Therefore, the treatment effect of OCS-sparing is captured through health state occupancy	Section B.3.3.6

Abbreviations: AEs: adverse events; CPRD: Clinical Research Practice Datalink; EGPA: eosinophilic granulomatosis with polyangiitis; eCVD: established cardiovascular disease; HRQoL: health-related quality-of-life; ICER: incremental cost-effectiveness ratio; IPD: individual patient data; IS: immunosuppressants; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; OCS: oral corticosteroid; RWE: real-world evidence; SF-36: Short Form 36-Item Health Survey; SMR: standardised mortality ratio; T2DM: type-2 diabetes mellitus; VDI: vasculitis damage index

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

Table 65: presents the *deterministic* base case results of the economic evaluation of benralizumab (at PAS price) as an add-on treatment to SoC, versus SoC. Over a lifetime horizon, benralizumab was associated with QALY gains of ■■■ QALYs per person and incremental costs of £■■■ per person, yielding an ICER of £25,314 per QALY gained. Benralizumab can therefore be considered a cost-effective treatment option and provides a positive NHB to the NHS at a willingness-to-pay threshold of £30,000/QALY, supporting the use of benralizumab for treating EGPA to improve population health.

Table 66 presents the *probabilistic* base case results of the economic evaluation of benralizumab, as an add-on treatment to SoC, versus SoC. Benralizumab was associated with a probabilistic ICER of £26,310 per QALY gained, falling within 4% of the deterministic ICER, indicating that cost-effectiveness results were largely insensitive to joint parameter uncertainty.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 65: Deterministic base-case results for benralizumab versus SoC (with PAS)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£25,314	0.245
SoC (OCS + IS)	██████	██████	██████	-	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; IS: immunosuppressants; LY: life years; NHB: net health benefit; OCS: oral corticosteroids; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care

Table 66: Probabilistic base-case results for benralizumab versus SoC (with PAS)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£26,310	0.187
SoC (OCS + IS)	██████	██████	██████	-	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; IS: immunosuppressants; LY: life years; NHB: net health benefit; OCS: oral corticosteroids; PAS: patient access scheme; QALYs: quality-adjusted life years

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.10 Exploring uncertainty

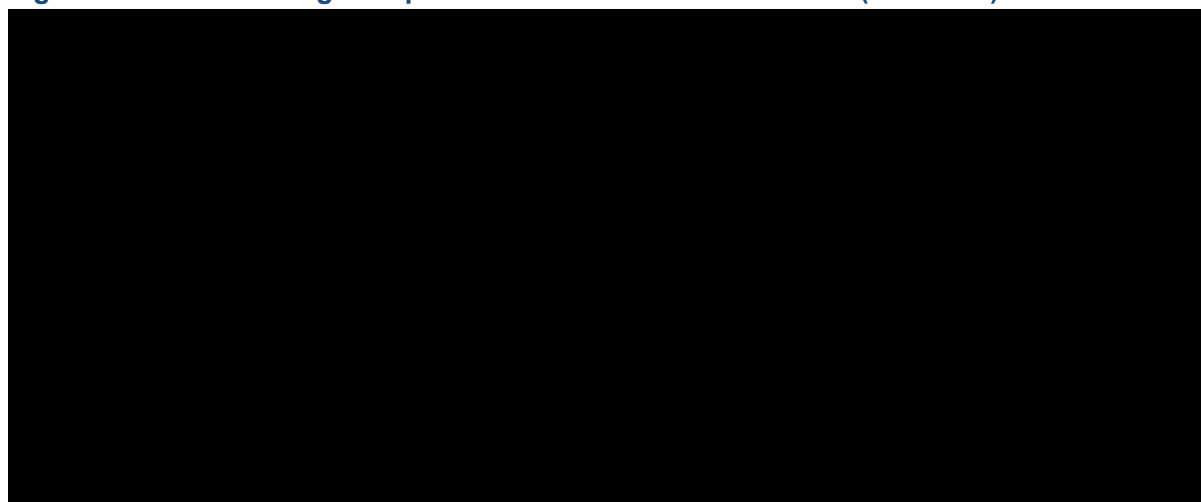
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses; the results of which are presented in Sections B.3.10.1 and B.3.10.2, respectively. In addition, key assumptions and alternative sources of input parameters in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.10.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. The values of the inputs were determined by random variation with statistical distributions as outlined in Table 63.

An ICER convergence plot, probabilistic cost-effectiveness plane and cost-effectiveness acceptability curve plot versus SoC are shown in Figure 16, Figure 17 and Figure 18, respectively. The ICER convergence plot demonstrates that 1,000 iterations were sufficient to achieve stability in the ICER. The probabilistic cost-effectiveness plane shows that the probabilistic iteration results are close to each other, and that the deterministic and probabilistic ICERs are similar. The probability that benralizumab was cost-effective versus SoC was predicted as 70.1% at a threshold of £30,000 per QALY (Figure 17), and the cost-effectiveness acceptability curve shows that this probability is >50% above a threshold of ~£26,000 per QALY (Figure 18).

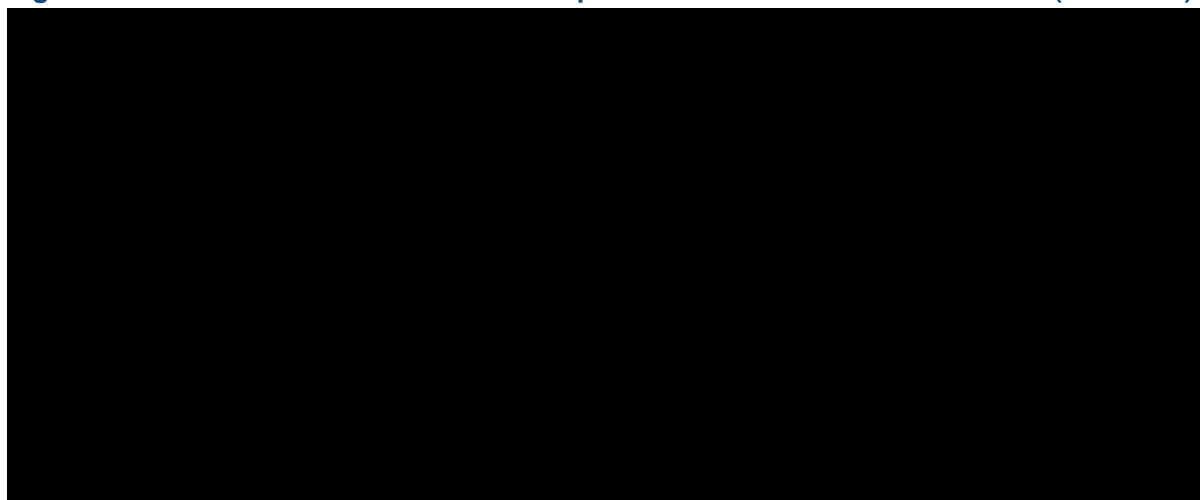
Figure 16: ICER convergence plot for benralizumab versus SoC (with PAS)



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PSA: probabilistic sensitivity analyses; QALYs: quality-adjusted life years.

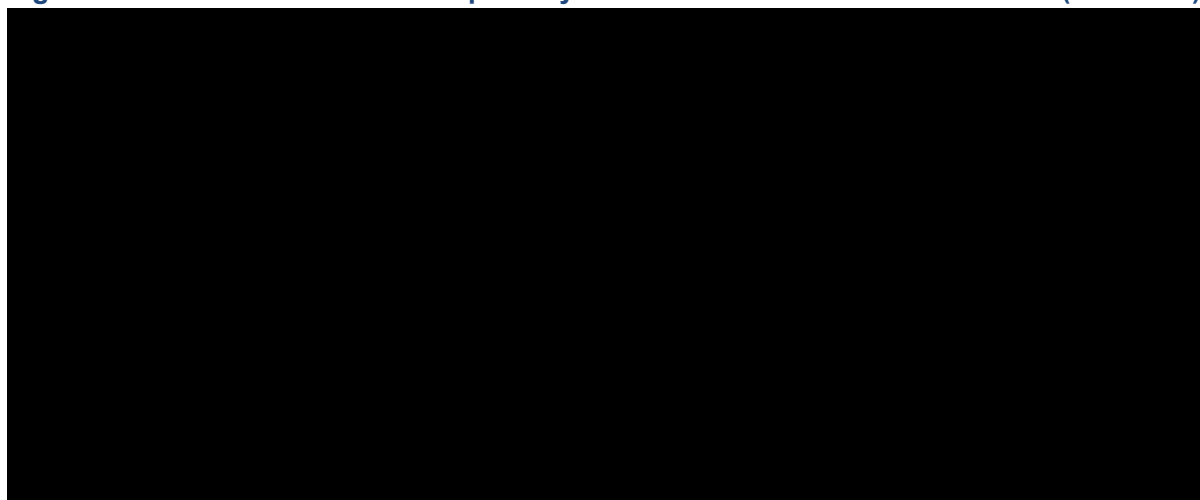
Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Figure 17: Probabilistic cost-effectiveness plane for benralizumab versus SoC (with PAS)



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PSA: probabilistic sensitivity analyses; QALYs: quality-adjusted life years.

Figure 18: Cost-effectiveness acceptability curve for benralizumab versus SoC (with PAS)



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PSA: probabilistic sensitivity analyses; QALYs: quality-adjusted life years.

B.3.10.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results and identify drivers of the ICER, DSA was conducted, in which individual inputs (Table 63, Section B.3.8.1) were varied whilst keeping all other model inputs constant. The parameters were varied by their 95% confidence intervals if the standard error was known; all other parameters were varied by +/- 20%.

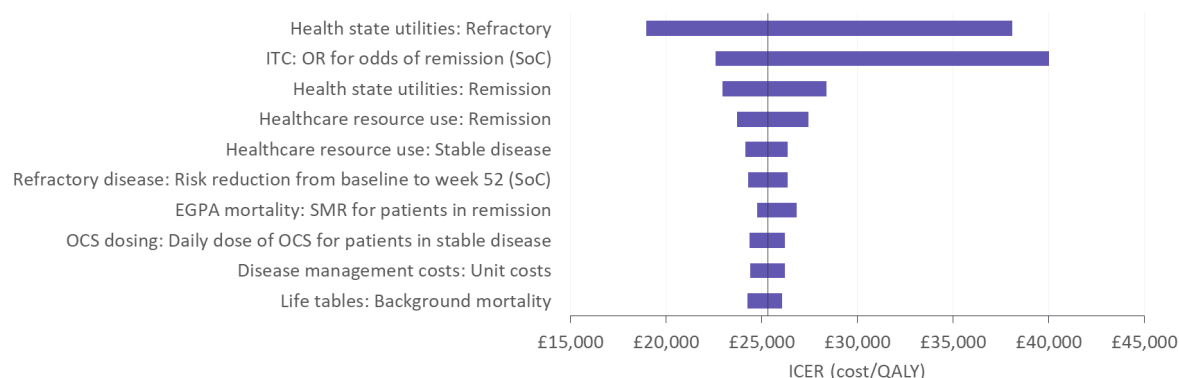
The impact of varying individual inputs on the ICER associated with benralizumab compared to SoC is shown in the form of a tornado diagram (Figure 19).

The inputs with the greatest impact on cost-effectiveness estimates was the refractory health state utility and the odds of achieving remission, derived from the Bucher ITC. Variation of the

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

remaining individual inputs did not have any substantial impact on cost-effectiveness estimates, showing the model to be largely robust to individual parameter uncertainty.

Figure 19: DSA tornado diagram for ICER for benralizumab versus SoC (with PAS)



Abbreviations: DSA; deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; OR: odds ratio; PAS: patient access scheme; QALYs: quality-adjusted life years; SMR: standardised mortality ratio; SoC: standard of care.

B.3.10.3 Scenario analysis

Several probabilistic scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model, as detailed in Table 62. Results of these scenario analyses are presented in Table 67.

Overall, the results of the scenario analysis were consistent with the results of the probabilistic base case analysis, demonstrating the results to be robust to uncertainties in the model inputs and assumptions. The ICER and NHB were most sensitive to the use of the general population and patient valuations from the vignette study, which resulted in an increase in QALYs. In all scenario analyses, benralizumab remained cost-effective compared to SoC at a willingness-to-pay threshold of £30,000/QALY.

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Table 67: Results of the scenario analyses (with PAS; probabilistic)

#	Base case input	Scenario analysis input	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£30,000)
Base case (probabilistic)			████	██	£26,310	0.19
1	Relative efficacy of benralizumab versus SoC informed by the Bucher ITC (Section B.2.9.1) - OR for remission: █████ - RR for ARR: █████	Relative efficacy estimates informed by MAIC (Appendix D) - OR for remission: █████ - RR for ARR: █████	████	██	£25,971	0.21
2	Health-state specific SMRs informed by CPRD - Remission: █████ - Stable disease: █████ - Relapse: █████	CPRD SMRs varied by +10%	████	██	£26,700	0.17
		CPRD SMRs varied by -10%	████	██	£25,846	0.21
3	█% annual discontinuation rate for benralizumab (based on conservative midpoint of alternative sources)	█% annual discontinuation rate (midpoint of sources in Document B, Table 41)	████	██	£25,056	0.22
4	Proportion of patients in refractory sub-state, within stable disease health state: - Benralizumab arm: Starting % of █████%, then relative reduction applied (informed by MANDARA) to yield █████% at week 52) - SoC arm: starting % of █████%, stayed constant (CPRD)	Starting proportion of patients in refractory sub-state, within stable disease health state -5%	████	██	£27,131	0.14
		Starting proportion of patients in refractory sub-state, within stable disease health state +5%	████	██	£25,556	0.23

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

5	Adelphi DSP study	General population valuation from vignette study	████	██	£16,049	1.16
		Patient valuation from vignette study	████	██	£13,654	1.60

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.

Abbreviations: ARR: annualised relapse rate; CPRD: Clinical Practice Research Datalink; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NHB: net health benefit; OR: odds ratio; PAS: patient access scheme; QALY: quality-adjusted life year; RR: risk ratio; SMR: standardised mortality ratio; SoC: standard of care

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.11 Subgroup analysis

As per the final scope from NICE for this evaluation, subgroup analyses are not relevant to this submission.

B.3.12 Benefits not captured in the QALY calculation

Benralizumab is anticipated to be associated with several benefits not captured in the QALY calculation, hence enhancing its value to the NHS:

- In the UK, there are currently no reimbursed treatment options indicated for EGPA. Of note, no submission was made to NICE for mepolizumab, an anti-IL-5 monoclonal antibody (mAb), meaning there are currently no effective biologic treatments available for all patients with EGPA. Therefore, national commissioning of benralizumab as a treatment for EGPA would result in improved access to effective treatment for all patients with EGPA, in line with the England Rare Diseases Action Plan 2024¹⁴⁰
- Further benefits which align with the England Rare Diseases Action Plan 2024 include increased awareness of EGPA for medical practitioners following a NICE recommendation.¹⁴⁰ With time, this could help streamline the care of EGPA patients and improve efficiency by reducing the time to diagnosis and thus improving coordination of care and reduce the use of HCP visits, with EGPA patients likely to see the correct medical practitioner more quickly
- EGPA causes progressive organ damage, creating significant long-term health consequences for patients. Consequently, patients with EGPA are at a high risk of heart disease, cardiomyopathy, respiratory failure and heart failure, with cardiac involvement associated with higher EOS counts. By depleting eosinophils and inducing sustained remission, benralizumab is expected to prevent further organ damage and reduce the risk of cardiac and respiratory involvement, slowing disease progression. This would increase the HRQoL of patients, as the symptom burden is decreased. This will also result in cost savings for the NHS, as patients will not need to be treated for progressive organ damage. This is evidenced by the stability in the vascular damage index (VDI) in the benralizumab arm during MANDARA.^{47, 83} However, in the absence of long-term evidence at the time of the cost-effectiveness analysis, a reduction in disease progression and long-term organ damage with benralizumab versus SoC was not modelled which can be considered a conservative approach
- Benralizumab induces sustained remission compared with SoC which is expected to allow patients with EGPA to self-administer benralizumab at home. This will result in cost savings to the NHS as well as benefits to patients, which have not been modelled in this cost-effectiveness analysis:
 - The increased convenience of homecare is expected to ease some of the financial burden of living with EGPA for patients, such as saving the time and cost of travel and reducing disruption to employment

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

B.3.13 Validation

B.3.13.1 Internal validation

Internal validation was carried out to assess whether outputs from the model (relapse and remission) were consistent with the data sources used to inform model development (see Appendix J).

B.3.13.2 External validation

To validate the economic model used in this submission, extensive feedback was gathered from clinical experts and health economic experts in the UK which was leveraged to finalise the model inputs.^{3, 78} Both clinical experts and health economic experts validated the model structure, model inputs and assumptions as being representative of patients with EGPA and of UK clinical practice, as detailed throughout this submission.^{3, 78}

B.3.13.3 Validation of Excel model

Model verification was carried out to assess the extent to which mathematical calculations were performed correctly and their consistency with the model's specifications, to ensure that there were no unintentional computational errors. Activities undertaken included:

- Extreme values analysis, to confirm that the model continues to yield appropriate results.
- Review of model equations and parameters against their source, to ensure that there are no transcription errors.
- Review of input derivation and implementation, to ensure that these have been derived and implemented correctly.

The model was subject to a rigorous review by health economists not involved in model development to ensure the model functioned as intended and generate accurate results which were consistent with input data and robust to extreme analyses. Furthermore, an extreme-value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model.

B.3.14 Summary

This submission seeks reimbursement for benralizumab as an add-on treatment to SoC, for adult patients with relapsing or refractory EGPA – in line with its full marketing authorisation.

Disease background & unmet need

EGPA is a rare, autoimmune condition, affecting a small population of approximately 2,600 people in the UK.^{15, 16} EGPA is a hypereosinophilic disorder, characterised by elevated circulating and tissue eosinophils, causing inflammation of small and medium-sized blood vessels, resulting in restricted blood flow and subsequent damage to multiple organs.^{17, 18}

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Severe, multi-system manifestations and organ damage have a considerable negative impact on patients' HRQoL.¹⁸⁻²⁰ The rarity of the disease, the lack of specialist expertise and symptom overlap with other conditions make diagnosis so challenging that it can take up to 12 years.^{38, 40}

Currently, there are no approved treatments in the UK, with high-dose OCS and IS being used as SoC in clinical practice.^{21, 26-28, 30} However, these therapies are sub-optimal. Firstly, both OCS and IS have limited effectiveness as demonstrated by high relapse rates and short times to relapse.³³⁻³⁵ Secondly, OCS is associated with multiple AEs while IS are toxic.

Clinical evidence

The pivotal, Phase III MANDARA trial met its primary endpoint, and demonstrated that treatment with benralizumab was efficacious with regards to durability of remission, low annual relapse rates and reductions or cessation of OCS use.¹

MANDARA was a pivotal active-controlled phase III trial offering head-to-head evidence for benralizumab versus mepolizumab – a gold standard in evaluating the effectiveness of treatments.¹ However, given that mepolizumab is not a reimbursed treatment option in the UK, comparative efficacy estimates had to be generated for the relevant comparator for this submission; UK SoC comprising of OCS and IS. In the ITC, benralizumab demonstrated a statistically significant improvement in the proportion of patients in remission and a reduction in annualised relapse rate, compared with SoC.

Cost effectiveness evidence

EGPA is a poorly characterised, given limited innovation and research in this space to date. Therefore, there is a scarcity of literature and no prior economic models to help inform the evolution of the disease. In light of this, AstraZeneca has undertaken extensive work to generate robust evidence to help inform decision making for the population of interest in this evaluation. The evidence strategy adopted for this submission was in line with the NICE RWE framework i.e. informing efficacy data from the RCT and informing other inputs using UK-relevant, EGPA-specific RWE. In addition, extensive discussions were conducted with clinical and health economic experts to validate the inputs and assumptions used. Finally, scenario analyses have been conducted to test the impact of these inputs and assumptions.^{3, 78}

The economic evaluation undertaken demonstrated that benralizumab is associated with a deterministic ICER of £25,314 per QALY gained. Benralizumab can therefore be considered a cost-effective treatment option at a threshold of £30,000 per QALY gained. The key drivers of the ICER included quality of life, relative efficacy and health care resource use. Overall, the results of the sensitivity and scenario analyses were consistent with the results of the probabilistic base case analysis, demonstrating the results to be robust to uncertainties in the model inputs and assumptions.

National commissioning of benralizumab would offer benefits not captured in the QALY by preventing future organ damage and thus, improving patients' long-term health. In addition, it would offer convenient management of the disease through self-administration minimizing impact of treatment on daily life. Finally, introducing a new treatment option should help to increase awareness of the condition and overall contribute to improved future management, aligned with the ambition set out in the England Rare Diseases Action Plan 2024.¹⁴⁰

Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

Conclusion

Providing access to benralizumab would be a paradigm shift in the management of EGPA in the UK, offering patients an efficacious alternative to the current sub-optimal SoC options. Clinical evidence and the economic case demonstrate that benralizumab would address a significant unmet need in this small, underserved patient population and constitute a cost-effective use of NHS resources.

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Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

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Company evidence submission for benralizumab with for treating adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (ID6266)

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Benralizumab for treating relapsing or
refractory eosinophilic granulomatosis with
polyangiitis [ID6266]**

Summary of Information for Patients (SIP)

November 2024

File name	Version	Contains confidential information	Date
ID6266 Benralizumab in EGPA SIP_27Nov24_[noCON]	1.0	No	27/11/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#).

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Benralizumab

Brand name: Fasenra®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

Benralizumab will be used for adults (aged 18 years or older) who are diagnosed with **relapsing** or **refractory** eosinophilic granulomatosis with polyangiitis (EGPA), receiving **oral corticosteroids (OCS)** with or without stable **immunosuppressive therapy (IS)**.

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressant; OCS: oral corticosteroid

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **marketing authorisation** (licence) for benralizumab is currently pending. More information on this can be found in **Document B, Section B.1.2**.

Broadly, the marketing authorisation is anticipated to be in line with the population of this submission, which is adults with relapsing or refractory EGPA.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK Limited engages with the following patient groups in this disease space to sponsor educational materials for clinicians and patients:

- American Partnership for Eosinophilic Disorders (APFED)
- Vasculitis Foundation
- International Eosinophil Society

Funding provided to UK patient groups is published annually on our website:

<https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups>

Abbreviations: APFED: American Partnership for Eosinophilic Disorders; UK: United Kingdom

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

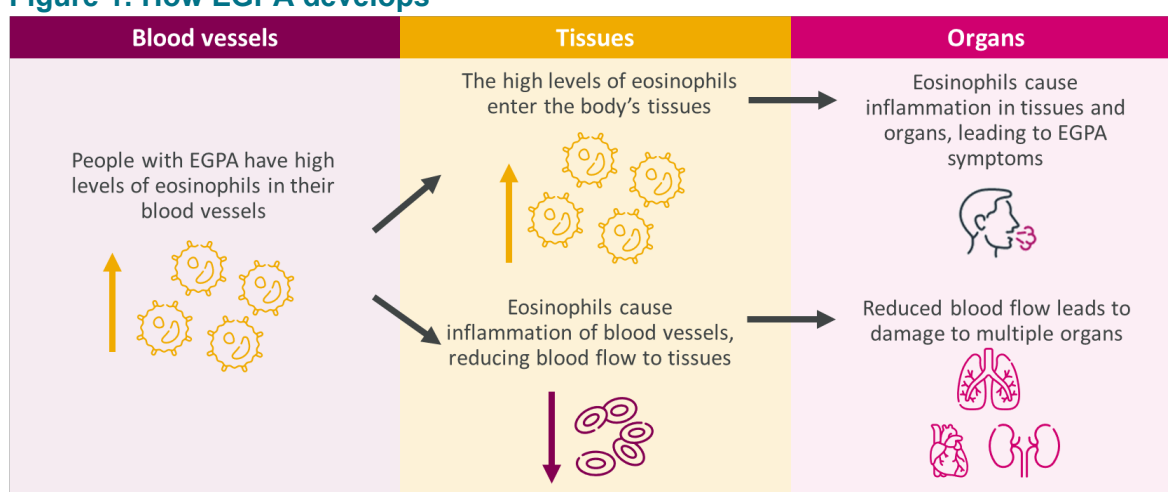
Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The main focus of this submission is for benralizumab treating EGPA

What is EGPA?

EGPA, previously known as Churg-Strauss Syndrome, is a rare condition caused by a high number of **eosinophils** (a type of white blood cell).¹ Normally, eosinophils help the **immune system** to fight infections. In EGPA, eosinophil levels are higher than normal. This leads to inflammation in **blood vessels**.¹ This inflammation restricts blood flow to tissues and organs throughout the body, causing a range of symptoms. If not treated correctly, the symptoms of EGPA can worsen over time and cause damage to organs (**Figure 1**).¹

Figure 1: How EGPA develops



How many people have EGPA?

Given that EGPA is a rare disease, there are limited publications available, but a recent UK-specific study estimated that 46 out of every one million individuals have EGPA in the UK. Therefore, there are approximately 2,600 people in England with EGPA.^{2, 3}

What are the symptoms of EGPA?

Patients with EGPA can have a variety of symptoms, some of these are shown in **Figure 2**. These symptoms are very diverse and can affect many different parts of the body.^{1, 4-8} As EGPA gets more severe, it can lead to heart failure, digestive issues, and weakness in limbs, loss of feeling, tingling or paralysis in areas of the body, resulting in difficulties with walking, standing, lifting and carrying objects.⁹⁻¹²

Figure 2: Common EGPA symptoms



Wheezing, coughing,
shortness of breath,
chest tightness



Difficulty with smell,
nasal congestion,
frequent sinus infections



Numbness and
tingling in the feet
and hands



Rashes, fever,
fatigue, pain, and
weight loss

How does EGPA progress?

EGPA develops in stages. Firstly, patients with EGPA may develop asthma, fatigue, pain, weight loss and fever. Following this, eosinophils attack organs, causing inflammation and organ damage.¹³

EGPA is best described by four **disease states**.

- **Remission** is when the disease is under control. Patients experience no symptoms or mild symptoms. Patients only need relatively small doses of medication to control inflammation.¹⁴ This is the “best” disease state for patients.
- **Relapse** is the re-appearance of EGPA symptoms that need to be managed by higher doses of medication.¹⁴ Patients in relapse experience more severe symptoms than those in remission.¹⁴⁻¹⁷

However, some patients have disease that does not quite fit into the definitions of remission or relapse. Instead, they have what is described as either **non-refractory** or refractory EGPA, which represents a disease spectrum.

- On the “better end” of the spectrum, there are patients with non-refractory disease. These patients’ disease has not quite achieved remission. Their symptoms are less severe than those in relapse and are reasonably well managed with stable doses of medication.¹⁸
- On the “worse end” of the spectrum, there are patients with refractory disease. These patients have not achieved remission in 6 months despite receiving high doses of medication and experiencing moderate to severe symptoms. Therefore, this is the “worst” of all disease states for patients.^{14, 16-18}

The non-refractory and refractory disease states are sometimes grouped into a single ‘**stable disease**’ state.

Impact of EGPA on quality of life

EGPA significantly affects the **quality of life** of patients. This is because the disease causes a range of debilitating symptoms and organ damage. EGPA symptoms and their impact on quality of life include:

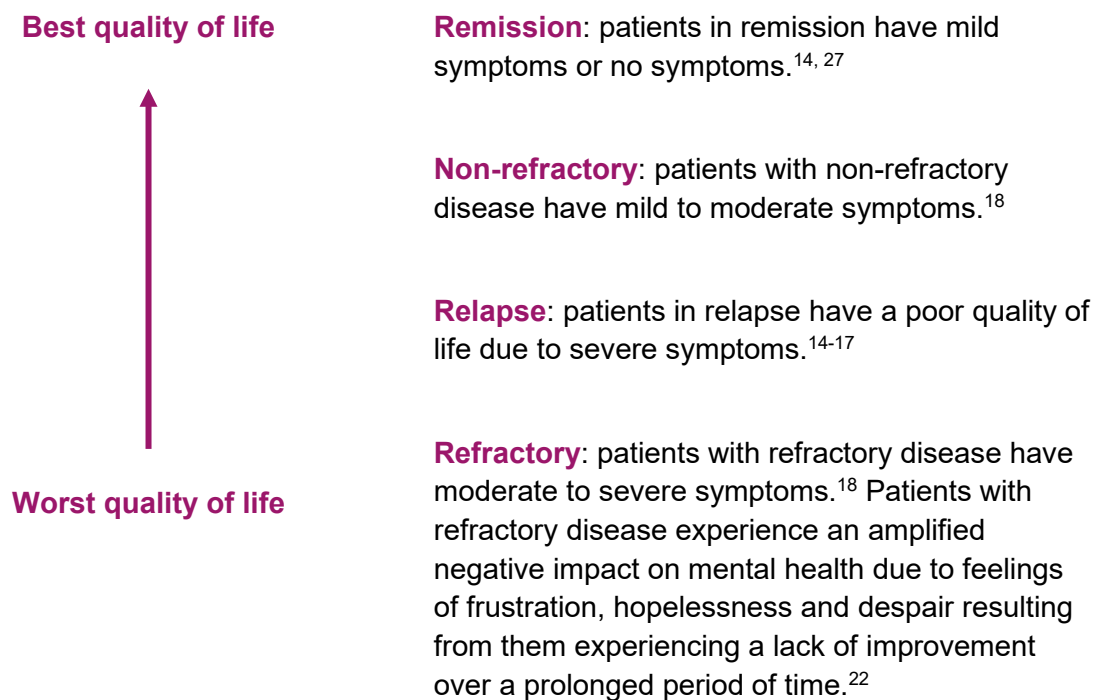
- Ear, nose and throat issues can disrupt sleep, and research shows that some people with these symptoms may go on to develop anxiety and depression.¹⁹
- Nerve problems, such as numbness or tingling in the hands and feet, can make it hard for people to do everyday tasks.^{11, 12}

- Coughing, wheezing and difficulty breathing can cause tiredness and affect multiple aspects of life, including work, education, social life and relationships.²⁰ These symptoms might also cause people to avoid social activities, making them feel isolated.²⁰
- Severe fatigue is also common in patients with EGPA.^{21, 22} This can reduce patients' ability to remain employed and live a "normal" life.²³

Patients have expressed the significant toll the disease takes on their mental health due to the severe symptoms of EGPA. EGPA can occur in cycles of remission and relapse; patients experience stress and anxiety as they go through cycles of their disease being controlled followed by periods where the disease is not controlled,^{24, 25} with frustration about how the illness impacts their lives.²⁶

According to patients and clinicians, the impact of EGPA on patients' lives can depend on their disease state (**Figure 3**).^{14, 27}

Figure 3: EGPA disease states



EGPA can also have a financial impact on individuals, as the disease can affect a person's ability to work, which can result in a loss of income. Patients may also face other financial challenges, including the cost of travelling to medical appointments.

Mortality

EGPA can reduce a patient's life expectancy.^{28, 29} Research shows that patients with EGPA are 2.3 times more likely to die in any time period, compared with the general public.³⁰ The risk of death can also vary by EGPA disease state: patients in relapse tend to have a shorter life expectancy than those in remission.³¹

Impact on families and carers of people with EGPA

Carers of patients with EGPA also experience an impact on their lives, for example:

- There is a financial impact because carers may need to take frequent time off from work to accompany patients to medical appointments and to care for patients.^{32, 33}
- There is a social impact because caring for someone with EGPA leaves carers with less time to work and socialise with others. This can lead to feelings of isolation and loneliness.³²
- Also, there is a psychological impact with carers experiencing negative impacts on their mental health as they worry about the future of their loved one.³² Social isolation can also have a psychological impact on carers.³²

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; UK: United Kingdom

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is EGPA diagnosed?

EGPA can be difficult to diagnose. This is because of its rarity and its broad range of symptoms, which can be similar to symptoms from other diseases.¹⁵ Patients often see multiple different medical practitioners for different symptoms before finally being diagnosed.¹⁵ This means patients have to wait up to 12 years between experiencing symptoms and getting a diagnosis.⁴

When patients present with symptoms, they will undergo a series of tests, including:³⁴

- Blood tests – to check the levels of eosinophils in the blood
- Chest X-ray – to check for lung damage
- Lung function – to check for asthma
- **Biopsy** – to check for tissue damage
- **Bronchoscopic lavage** – to check the levels of eosinophils in the lungs
- Heart test – to check for heart damage

These tests help doctors reach a definitive diagnosis.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

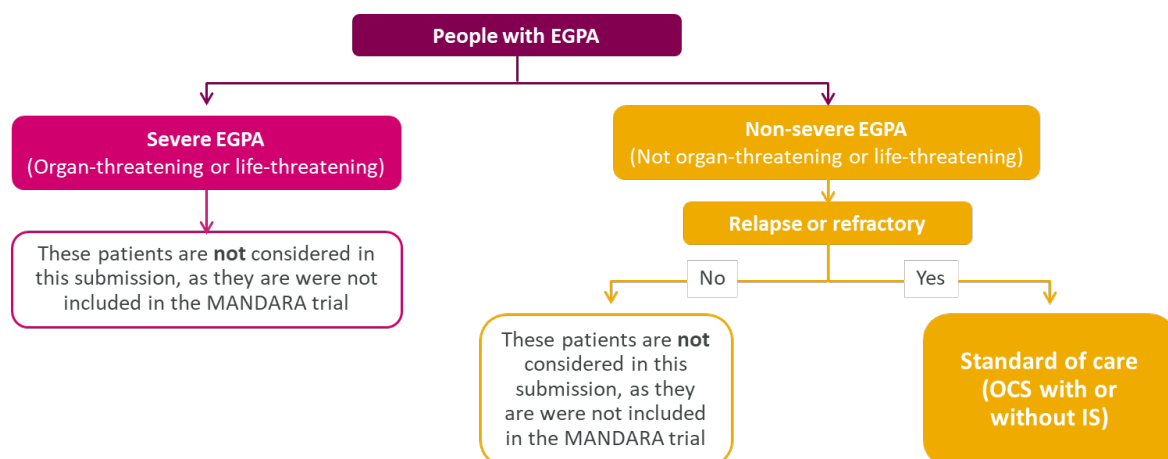
How is EGPA currently treated in the UK?

Standard of care (oral corticosteroids + immunosuppressants)

The goal of EGPA treatment is to reduce eosinophil levels to help suppress the immune system and control inflammation. This would allow patients with EGPA to experience remission.¹⁴

There are currently no treatments approved for EGPA available on the National Health Service (NHS). The current **standard of care** for EGPA is oral corticosteroids (OCS) with or without immunosuppressants (IS). For the rest of this document, standard of care refers to OCS with or without IS. OCS are sometimes simply referred to as “steroids”. **Figure 4** shows which patients this submission is relevant to.

Figure 4: Treatments available for EGPA, relevant to this submission



OCS can reduce inflammation and may help some patients achieve remission.¹⁴⁻¹⁷ It has been found that OCS were prescribed in the vast majority of patients with EGPA in England.³⁵ Sometimes, OCS need to be combined with IS to help patients achieve remission.¹⁴ IS do not target eosinophils but are powerful at suppressing the immune system. The most commonly prescribed IS are called azathioprine, methotrexate and mycophenolate mofetil.^{16, 35}

However, the current standard of care options are limited and sub-optimal. Patients often need to take high doses of OCS to reduce the high levels of eosinophils associated with EGPA.³⁵ However, high daily OCS doses can cause important **side effects** for patients.¹ OCS can cause weight gain, heart conditions, depression, diabetes and **osteoporosis**.^{1, 36, 37} IS are also associated with a high risk of organ toxicity and side effects, including **cytopenia, hepatotoxicity**, and major infections.^{14-17, 36, 37}

In addition, OCS and IS treatments are associated with high relapse rates and are not effective in maintaining remission. Up to 82% of patients, receiving OCS with or without IS, who achieve remission will experience relapse and its associated symptoms within less than one year on average.³⁷⁻³⁹ High relapse rates from OCS and IS have a two-fold implication. Firstly, relapsed disease is treated with increased doses of OCS and IS, which further increases the risk of OCS-related and IS-related side effects.^{1, 36, 37} Secondly, the cycles of their disease being controlled followed by periods where the disease is not controlled cause patients to feel low, scared, frustrated and anxious, amplifying negative feelings about future outcomes.²²

There is an unmet need for a well **tolerated** treatment which can help patients achieve and maintain remission. This will allow patients to reduce OCS doses, hence avoiding the significant side effects associated with its use.

Cyclophosphamide

Cyclophosphamide is mainly used in patients with life-threatening or organ-threatening EGPA (referred to as 'severe EGPA').¹⁴⁻¹⁷ Cyclophosphamide is toxic to organs and can cause infertility,^{40, 41} hence why doctors prefer to limit its use to patients with severe EGPA. This submission does not cover patients with life-threatening or organ-threatening EGPA, as shown in **Figure 4** – therefore, cyclophosphamide is a not relevant alternative to benralizumab.

Rituximab

Rituximab is sometimes used in patients with life-threatening or organ-threatening EGPA, who are not included in this submission.^{14, 16, 17} Additionally, doctors have confirmed that rituximab is not routinely used in the UK.¹⁸ Therefore, rituximab is not a relevant alternative to benralizumab.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressants; NHS: National Health Service; OCS: oral corticosteroids; UK: United Kingdom

2d) Patient-based evidence (PBE) about living with the condition

Context:

- Patient-based evidence (PBE) is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about patient needs and disease experiences. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

EGPA from the patient perspective

As discussed in [Section 2a](#), EGPA can have a negative impact on patients' quality of life. The symptoms of EGPA can make it difficult to carry out daily activities, socialise, exercise and work.²⁰ Each disease state impacts quality of life for patients to a different extent as shown in [Figure 3](#). Patients with refractory disease tend to have the worst quality of life while patients in remission tend to have the best quality of life. Also, patients with EGPA cycle through different disease states which impact their mental wellbeing, resulting in stress and anxiety.

AstraZeneca conducted in-depth interviews with patients and doctors to gain a better understanding of what it is like to live with EGPA. Based on patient interviews, there were some particular challenges they were facing:

Fatigue

Patients expressed that fatigue impacted their ability to exercise and perform routine tasks:⁴²

"I experienced fatigue and EGPA impacted my ability to exercise"
"Showering on a daily basis was exhausting"
"I couldn't walk upstairs"

Impact on mental health

Patients also expressed the impact of EGPA on their mental health.⁴² Patients discussed feeling isolated, living in fear of potential relapse and worsening symptoms.⁴² These negative feelings have a large impact on the mental and physical health of patients with EGPA. These feelings are more intense in patients with refractory EGPA, whose disease is not being controlled. Some patients noted:⁴²

"It is an anxiety inducing condition"
"I was in a bad mental health space"
"I feel detached from others"

Impact on social life

A study identified the impact of EGPA on social life, with a patient expressing:⁴³

“I’ve withdrawn from people and seldom go out (...), preferring to talk by text, email and chat. I can’t concentrate on work. I feel distant from my husband. I’ve found it very difficult to talk to friends, they don’t quite understand”

Coping with treatment

Furthermore, patients have shown concern over the long-term use of OCS and the side effects they cause:^{42, 43}

“I have been reduced it (sic) steroid tablets but am concerned about all the side effects from the medications. I have started to get joint [pain] and particularly in the knees and elbow. I am taking several medications to combat steroid side effects.”

“[I] worry about the side effects of my treatments, particularly the steroids”

“[the] biggest challenge becomes the drugs and not the condition itself”

“I’m keen to get off steroids”

Patients have expressed a need for a successful treatment which reduces EGPA symptoms in the same way as OCS but without their harmful side effects:⁴²

“Having something that is new, has a greater positive impact on my condition and is less harmful would be amazing”

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroids; PBE: patient based evidence

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

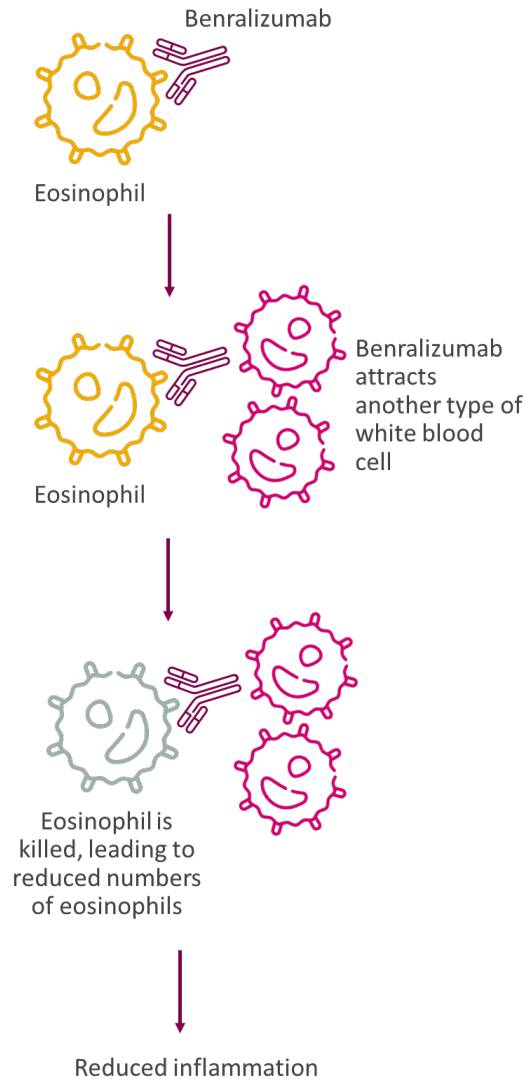
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

About benralizumab and how it works

As mentioned above, EGPA is caused by a high number of eosinophils. The way benralizumab works is shown in **Figure 5**. Benralizumab is a **monoclonal antibody** that specifically attaches to eosinophils. Once attached, it attracts another type of white blood cells which kill the eosinophils.⁴⁴⁻⁴⁶ This reduces the levels of eosinophils in the body, which is the goal of EGPA treatment. As a result, inflammation is reduced.⁹

Figure 5: How benralizumab works



Benralizumab is expected to be used alongside standard of care (OCS with or without IS) for patients with relapsing or refractory EGPA.¹⁸

Benralizumab is currently approved in the UK for the treatment of severe asthma.⁴⁷

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressants; OCS: oral corticosteroids; UK: United Kingdom

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Benralizumab will be used as an add on to standard of care (**Section 3a**).⁴⁸ Patients are generally not expected to take other medicines alongside benralizumab and standard of care (OCS with or without IS). An important goal of treatment with benralizumab is to reduce the use of OCS because they are associated with harmful side effects and do not successfully control the disease (as described in **Section 2c**).

Abbreviations: IS: immunosuppressants; OCS: oral corticosteroids

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is benralizumab taken for EGPA?

Benralizumab is taken as an injection (FASENRA Pen®).⁴⁹ Benralizumab is injected under the skin (**subcutaneously**). This can be administered by a healthcare provider. Over time, once patients reach remission, benralizumab can be administered by patients themselves or caregivers at home, after receiving training.⁴⁹

How much medicine do patients take and when?

It is expected that patients with EGPA will take 30 milligrams (mg), a single injection of the FASENRA Pen®, of benralizumab every 4 weeks.⁴⁸

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; mg: milligram

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of benralizumab in EGPA

The primary **clinical trial** assessing benralizumab for the treatment of EGPA is the MANDARA trial.⁵⁰ A summary of the key information for MANDARA is provided in **Table 1**.

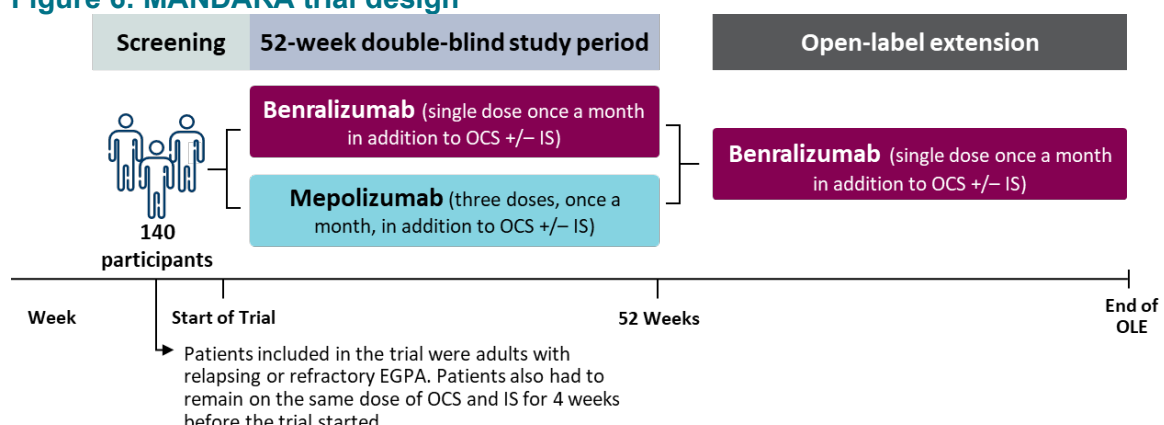
The MANDARA trial was a **Phase 3 trial**. This means the trial assessed how well benralizumab worked to treat EGPA (its **efficacy**) and how safe the medicine was, compared to another treatment called mepolizumab. Mepolizumab is another monoclonal antibody that can be used to treat EGPA, but it is not available in the UK.⁵¹

Table 1. Trial investigating benralizumab for EGPA

Trial name and number	Phase 3, MANDARA (NCT04157348) ⁵²
Location	North America Europe Asia
Patient population	Adults (over 18 years old) with relapsing or refractory EGPA. Patients also had to remain on the same dose of OCS and IS for 4 weeks before the trial started.
Number of patients included	140

Figure 6 shows how the trial was carried out. The trial consisted of two main periods. Patients were randomly assigned to take either benralizumab or mepolizumab for one year (this is called the **double-blind** period where participants and researchers do not know what treatment each participant is receiving). After that year, patients could continue taking benralizumab for another year (this is called the **open-label** period where both the participants and researchers know which treatment is being given to each participant).⁵⁰

Figure 6: MANDARA trial design⁵⁰



Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressants; NHS: National Health Service; OCS: oral corticosteroids

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How was the efficacy of benralizumab in EGPA measured in the trial?

The key efficacy results of MANDARA after one year of treatment are shown in **Figure 7**.⁵⁰

Figure 7. Key efficacy results for MANDARA⁵⁰

	
58% of patients treated with benralizumab were in remission at both 36 and 48 weeks. This means no active EGPA disease activity and daily OCS use of 4 mg or less	41% of patients receiving benralizumab no longer required OCS
Versus 57% of patients in the group receiving mepolizumab	Versus 27% of patients in the group receiving mepolizumab
	
85% of patients receiving benralizumab reduced their dose of OCS by 50% or more	Patients treated with benralizumab had a relapse rate of 1 relapse every 2 years , with 70% of patients relapse free
Versus 74% of patients in the group receiving mepolizumab	Results for patients treated with mepolizumab were similar

More efficacy results can be found in **Document B, Section B.2.6**.

Comparison of benralizumab to standard of care

The MANDARA trial did not compare benralizumab to UK standard of care (OCS with or without IS). To compare benralizumab versus standard of care, an **indirect treatment comparison** (ITC) was required. An ITC is a way to compare the effects of different treatments that were not included in the same study. MANDARA compared benralizumab to mepolizumab. Another trial called MIRRA compared mepolizumab to standard of care. Therefore, mathematically combining the results of the MANDARA and MIRRA trials produced a comparison of benralizumab to standard of care.

Results of the ITC showed that benralizumab was better than standard of care in helping patients achieve remission and avoid relapse.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; ITC: indirect treatment comparison; OCS: oral corticosteroids

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQoL-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Impact of benralizumab on quality of life

Throughout MANDARA, patients were asked to answer questions about their quality of life, using various questionnaires. Patients receiving benralizumab showed similar improvements in quality of life between the start and end of the trial compared with people receiving mepolizumab.⁵⁰ Two other real world studies (known as the **Adelphi disease-specific programme [DSP]** and a UK-specific **vignette study**) confirmed that remission and non-refractory disease are associated with a better quality of life than refractory disease or relapse.^{22, 53} Therefore benralizumab treatment, which helps patients achieve remission, could be expected to improve their quality of life.

Abbreviations: DSP: decision support platform

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Side effects of benralizumab

Every medicine has the potential to result in side effects, and the same medicine can produce different reactions in different people. In MANDARA, benralizumab was well tolerated.⁵⁰

The most common side effects experienced by patients receiving benralizumab in MANDARA was COVID-19, followed by headaches. The trial was conducted between 2019 and 2023, during which time the COVID-19 pandemic took place. This likely contributed to the high number of COVID-19 events. Side effects observed in more than 3% of patients in any group in MANDARA are summarised in **Table 2** below.

Table 2. Summary of the most common side effects experienced by patients during MANDARA

Side effect	Percentage of patients with side effect	
	Benralizumab	Mepolizumab
COVID-19	21.4%	27.1%
Headache	17.1%	15.7%
Arthralgia	17.1%	11.4%
Nasopharyngitis	8.6%	14.3%
Sinusitis	7.1%	11.4%
Fatigue	7.1%	8.6%
Bronchitis	7.1%	7.1%
Bacterial sinusitis	7.1%	4.3%

Note: further explanation of the terms in **bold** are provided in the glossary (**Section 4b**).

No deaths occurred in the double-blind part of the trial. There was one death in the open-label part of the trial of a patient who was receiving mepolizumab and then switched to benralizumab. This death was not related to treatment.⁵⁰

Benralizumab was approved for the treatment of severe asthma in 2019⁵⁴ and has been used by many patients since then. In MANDARA, no new side effects were discovered with benralizumab when it was used to treat EGPA at the higher dose (the dose of benralizumab in EGPA is twice that used in severe asthma).⁵⁰

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

At present, the treatment options for people with EGPA are limited and sub-optimal. The key benefits of benralizumab for patients with EGPA are presented below:



Benralizumab would represent the first treatment approved for EGPA in the UK



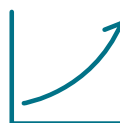
Benralizumab has been shown to help patients reach, and remain in, remission as well as avoid relapses.⁵⁰ Patients in remission have a greater quality of life than those in relapse so receiving benralizumab results in an improvement in quality of life¹⁴



Patients treated with benralizumab had reduced eosinophil levels so were able to reduce their OCS dose or even stop taking OCS.⁵⁰ This may result in a reduction in the new occurrence of negative side effects and chronic disease associated with these treatments



Treatment with benralizumab is well tolerated in patients with EGPA, with low levels of unexpected side effects experienced by patients in the MANDARA trial⁵⁰



Benralizumab is taken as a prefilled syringe. This offers convenient injection options including the ability for patients or caregivers to administer the pen themselves at home after receiving training.⁴⁹ This convenience is expected to ease the financial burden associated with EGPA, for example reduced disruption to patients' employment and cost of travel to hospitals



Benralizumab has been shown to improve patient outcomes by providing durable remission and reducing relapse rates in patients with EGPA, as described in **Section 3e**.⁵⁰ As relapses contribute to organ damage, treatment with benralizumab may prevent further organ damage

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; NHS: National Health Service; OCS: oral corticosteroids; UK: United Kingdom

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Like all medications, benralizumab can cause side effects. However, the treatment was generally well tolerated.⁵⁰ The main side effects associated with benralizumab are listed in **Section 3g**.

In the MANDARA trial, patients taking benralizumab reported higher rates of headaches, arthralgia (joint pain) and bacterial sinusitis (sinus infections) compared with mepolizumab, but these were low in severity.⁵⁰

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (benralizumab) with standard of care (OCS with or without IS). This analysis is conducted in the relevant patient population (adults diagnosed with relapsing or refractory EGPA, receiving OCS with or without stable IS). This analysis helps determine if benralizumab used to treat EGPA would be a good use of NHS resources.

How the model reflects EGPA

The economic model was designed to reflect the natural evolution of EGPA and clinical practice in the UK. The model focused on the comparison on benralizumab versus standard of care (OCS with or without IS) in patients with EGPA.

The model included the following disease states: remission, stable disease, relapse and death. These disease states were selected to mirror the experience of patients with EGPA over their lifetime.

In the model, all patients began in a 'stable disease' state (comprised of refractory and non-refractory patients). The stable disease state mirrored patients who entered the MANDARA trial (as described in [Section 3d](#)). Each month, patients could move between disease states or stay in their current disease state. This reflected whether they entered remission, experienced a relapse or remained in stable disease. The movement of patients from relapse and stable disease to the remission state indicated a successful outcome in the model.

Disease states were associated with different healthcare resource use costs and quality of life.

Modelling the effectiveness of benralizumab

The results of the MANDARA trial and the indirect treatment comparison informed how patients moved between the disease states in the economic model. The rates of remission and relapse from the MANDARA trial informed the chances that patients receiving benralizumab would remain in their disease state or move to a different disease state. Results from the ITC, discussed in [Section 3e](#), informed the same movements for patients receiving standard of care.

The ITC results showed that patients receiving benralizumab were more likely to enter remission and less likely to experience a relapse, compared with standard of care. This was reflected in the model with patients in the benralizumab arm being more likely to remain in the remission state and less likely to enter the relapse state, compared to standard of care.

Prescription data from real world patients with EGPA in England informed the OCS doses received. Patients in remission received the lowest OCS dose and patients in relapse received the highest. As benralizumab was associated with greater remission rates (and lower relapse rates) than standard of care, benralizumab was indirectly associated with lower OCS doses in the model. The negative impact and costs of the side effects associated with OCS treatment on health were also considered in the model. Therefore, the costs and negative impact on quality of life associated with OCS-related side effects were overall lower for patients receiving benralizumab compared with standard of care.

Modelling how much benralizumab improves clinical outcomes

To accurately reflect possible disease progression, patients could die at any point in the model, due to EGPA or any other cause. The effect of benralizumab on survival was not directly modelled. Instead, each disease state was associated with a different risk of death. The remission state was associated with the lowest risk of death while the relapse state was associated with the highest risk of death. Benralizumab was associated with a higher chance of remaining in the remission state and less chance of relapse, compared

to standard of care. Therefore, the risk of death was overall lower for patients receiving benralizumab compared with standard of care.

Modelling how much benralizumab improves quality of life

The quality of life data used in the model were from an Adelphi disease-specific programme study. In the Adelphi DSP, patients with EGPA completed questionnaires about their experience with the disease and their quality of life. The response to the questionnaires was then used to assign a numerical value on quality of life, which was different for each EGPA disease state.

The results showed that patients with refractory disease tend to have the worst quality of life while patients in remission tend to have the best quality of life.⁵³ This reflected the fact that the symptom burden, mental and emotional impact of EGPA would likely be reduced when a patient experienced remission.

Therefore, an improvement in quality of life was modelled when a patient experienced remission. As treatment with benralizumab is associated with a higher chance of experiencing remission, patients experience an overall better quality of life.

Modelling how the costs of treatment differ with benralizumab

Benralizumab was more expensive than standard of care (OCS with or without IS) when costs over a patient's lifetime were considered. However, benralizumab offered increased survival and quality of life for patients with EGPA.

Various NHS costs were included in the model. These costs included:

- The cost of benralizumab
- The cost of OCS and IS
- The cost of monitoring patients with EGPA (e.g. GP or hospital visits)
- The cost of treating side effects of OCS treatment, such as diabetes, heart conditions and osteoporosis

Benralizumab may result in cost savings for the NHS compared to OCS and IS for patients with EGPA. This is because patients receiving benralizumab were more likely to be in remission compared to patients receiving standard of care. Costs in the remission state were less compared to other disease states for these reasons:

- Reduced requirement for medical visits (e.g. GP consultations or hospitalisation)
- Lower OCS dose required so reduced costs associated with treating and managing OCS side effects

Uncertainty

Due to the rarity of EGPA and hence limited literature, new UK-specific real-world evidence was generated to inform this submission. These data were validated by EGPA clinical experts.¹⁸

As is the case for any economic model, there were various assumptions that were made in the analysis. Information on these assumptions can be found in **Document B, Section B.3.8.2**. All assumptions were sense-checked by EGPA clinical experts. A variation of model inputs was tested, and the results of these tests are explained in **Document B,**

Section B.3.10. Overall, the cost-effectiveness results did not change significantly when alternative inputs were used, which means that the results were robust.

Benefits of benralizumab not captured in the economic analysis

Treatment with benralizumab may have many different positive impacts for patients with EGPA and for the NHS. By preventing relapses and allowing durable remission,³⁹ benralizumab may save important resources in hospitals, such as the time of nurses, pharmacists and doctors. The model aimed to capture as many of these benefits as possible, but there were other benefits that could not be fully captured. For example:

- The approval of benralizumab is expected to increase awareness of EGPA among healthcare professionals. With time, this could help reduce the time to diagnosis and improve the quality of care for patients with EGPA
- As benralizumab can be self-administered at home, patients can benefit from reduced costs from less frequent travel to healthcare facilities and not having to take time off work
- Benralizumab is expected to prevent further organ damage and reduce disease progression. This was not modelled because of limited long-term evidence

Conclusions

This section provides an overview of the modelling performed by AstraZeneca. However, AstraZeneca's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions which are different from the assumptions that the company used in their model.

Given this, AstraZeneca has not presented any specific cost-effectiveness results in this summary, but it should be noted that the final cost-effectiveness results for this submission will be discussed in the Committee meeting and will be available on the NICE website once a final decision is made.

Abbreviations: DSP: decision support platform; EGPA: eosinophilic granulomatosis with polyangiitis; GP: general practitioner; IS: immunosuppressants; ITC: indirect treatment comparison; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; OCS: oral corticosteroids; UK: United Kingdom

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any **QALY** benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Benralizumab is a new and innovative treatment, and would represent an important advancement in the treatment of EGPA

EGPA is a rare, inflammatory condition.¹ It causes a range of symptoms and can lead to organ damage.¹ EGPA also has a substantial negative impact on the quality of life of patients.²²⁻²⁴ There are currently no treatments for EGPA available on the NHS. The current standard of care for EGPA are OCS and IS, however these do not control the disease adequately and are associated with severe side effects.^{1, 14-17, 36-38}

Benralizumab would represent the first treatment approved for EGPA in the UK. Benralizumab has a unique and targeted mechanism of action, focusing on reducing eosinophil levels.³⁹ This would represent an advancement in the treatment of EGPA.

Benralizumab treatment would offer patients durable remission, while allowing them to reduce or stop OCS use,³⁹ which may help to reduce new OCS-related side effects. Benralizumab would also provide patients with the opportunity to experience reduced symptoms and it may prevent further organ damage.³⁹ This could reduce the negative impact that EGPA has on patients' lives.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressants; NHS: National Health Service; OCS: oral corticosteroids; UK: United Kingdom

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

[Find more general information about the Equality Act and equalities issues here](#)

Some patients with EGPA have severe eosinophilic asthma. Patients with severe eosinophilic asthma are eligible for treatment with benralizumab. This poses an equality consideration for the following reasons:

- Not all patients with EGPA have severe eosinophilic asthma^{5, 55, 56}
- Patients with EGPA and severe eosinophilic asthma would only receive benralizumab if they met the eligibility criteria for its recommendation within severe eosinophilic asthma
- Access to severe asthma centres in England (where benralizumab is prescribed for severe asthma) is challenging
- If patients with EGPA and severe eosinophilic asthma access benralizumab, the dosing schedule prescribed will be for severe eosinophilic asthma, which is less frequent than the dosing schedule for EGPA. This less frequent asthma dosing has not formally been tested in EGPA. More frequent dosing is considered necessary for EGPA because it is a more severe disease than asthma, and eosinophil levels are often higher.

Therefore, AstraZeneca firmly believes that benralizumab should be made available for **all** eligible patients with EGPA, at the dose that was investigated and proved to be effective.

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information on EGPA:

- [Churg Strauss Syndrome - Vasculitis UK](#)

Further information on MANDARA trial

- [ClinicalTrials.gov](#)

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

Abbreviations: EFPIA: European Federation of Pharmaceutical Industries and Associations; EGPA: eosinophilic granulomatosis with polyangiitis; EUPATI: European Patients' Academy on Therapeutic Innovation; HTA: Health Technology Assessment; INAHTA: International Network of Agencies for Health Technology Assessment; NICE: National Institute for Health and Care Excellence; UK: United Kingdom; VCS: voluntary and community sector

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Adelphi Disease-Specific Programme	Detailed insights from healthcare professionals and patients to help understand more about specific diseases in the real world
Arthralgia	Discomfort, pain or inflammation of joints
Bacterial sinusitis	When sinuses (spaces near your nose) become swollen due to a bacterial infection
Biopsy	A small sample of tissue is taken from the body and examined under a microscope
Blood vessels	Tube-like structures that carry blood around the body. Arteries, veins and capillaries are all types of blood vessels. Together, they form a network that moves blood around your body
Bronchitis	Occurs when the tubes that carry air to the lungs become inflamed
Bronchoscopic lavage	A tube is inserted into the lungs. Fluid is put into the tube and enters a part of the lung. This fluid is then collected back for analysis
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study
Cytopenia	A condition where patients have a lower-than-normal number of blood cells. This can

	lead to tiredness, increased chance of infection and bruising easily
Disease state	The condition of a person's health related to the severity of their EGPA. Disease states in EGPA include remission, non-refractory disease, refractory disease and relapse
Double-blind	The participants and researchers do not know what treatment each participant is receiving
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial
Eosinophils	A type of white blood cell that has an important role in the immune system . They are usually present in small numbers and respond to allergic reactions and infection. In EGPA, there are high numbers of eosinophils
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial
Hepatotoxicity	Another name for liver damage. Symptoms of hepatotoxicity may include fatigue, sickness and stomach pain
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases
Immunosuppressants or immunosuppressive therapy	These are drugs that help lower or suppress the activity of the body's immune system

Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country
Monoclonal antibody	A protein that can target specific cells in the body to help treat diseases
Nasopharyngitis	An infection of the nose and throat. Otherwise known as the “common cold”
Non-refractory	Patients are on stable doses of medication and see an improvement in their disease
Open-label	Both the participants and researchers know which treatment is being given to each participant
Oral corticosteroids	These are medications that help reduce inflammation and suppress the immune system
Osteoporosis	A health condition that weakens bones, making them fragile and more likely to break
Phase 3 clinical trial	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are

	calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living
Refractory	Patients have not had remission for the previous 6 months. They have severe symptoms. They are on high doses of medication
Regulatory body	These are legal bodies that review the quality, safety and efficacy of medicines and medical technologies
Relapse	Patients' symptoms get worse and require high doses of medication
Remission	When a disease is under control and there are no symptoms or mild symptoms
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe
Sinusitis	When sinuses (spaces near your nose) become swollen and inflamed
Stable disease	A disease state for patients who are not in relapse or remission. This state is made

	up of a group of patients who have refractory or non-refractory disease
Standard of care	For EGPA, standard of care refers to oral corticosteroids and immunosuppressants. These are the most commonly used treatments for EGPA in UK clinical practice
Tolerated	The ability of a patient to put up with the side effects of treatment
Vignette study	A research method that uses short descriptions of disease states to explore how they impact patients' quality of life

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Clarification questions

17th January 2025

File name	Version	Contains confidential information	Date
ID6266 Benralizumab in EGPA Clarification Questions Response_30Apr25_[NoCON]	0.2	No	30/04/2025

Section A: Clarification on effectiveness data

A1. Literature searches

Please cite any search filters used in the clinical effectiveness searches, reported in Appendix D of the company submission (CS).¹

The search terms to identify randomised clinical trials (RCTs) were based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials.² Observational studies were identified using a filter developed by the Scottish Intercollegiate Guidelines Network (SIGN).³

Broad disease area search terms were designed by an information specialist to include a range of terms that may be used to accurately describe eosinophilic granulomatosis with polyangiitis (EGPA), whilst ensuring sensitivity and specificity of the search strategy and minimising the risk of missing relevant publications. The disease area search terms were similar to those used in a published systematic review of EGPA.⁴ Search terms relating to relevant concepts were identified through discussion within the research team, scanning background literature and browsing database thesauri. Searches were scoped in Ovid Embase (the most comprehensive database).

A2. Disease states

Priority question: Refractory and non-refractory are labelled as ‘stable disease’ in the CS.⁵ In the CS (Appendix O),⁶ the company details vignette descriptions of disease states. [REDACTED]

[REDACTED]

[REDACTED].

- a) Please explain [REDACTED]
[REDACTED], and therefore the difference
between the refractory and relapse states.

Re-cap of key context

Disease states in EGPA

EGPA is best described by four disease states outlined below (see Figure 1):

- **Remission (A)** is when the disease is under control. Patients experience no symptoms or mild symptoms. Patients only need relatively small doses of oral corticosteroid (OCS) to control inflammation. This is the “best” disease state for patients.
- **Relapse (B)** is an episode of significantly worsening symptoms requiring an escalation in treatment (increase in OCS dose) or hospitalisation. Patients in relapse experience more severe symptoms than those in remission.

- **Non-refractory (C)** is when patients' disease has not achieved remission, but their symptoms are less severe than those in relapse and are reasonably well managed with stable doses of OCS; their condition remains mostly unchanged and may even improve slowly.
- **Refractory (D)** is when patients have not achieved remission in six months despite receiving high doses of OCS and experiencing moderate to severe symptoms. This is the "worst" of all disease states for patients, because although symptom burden can be lower than in a relapse, this state lasts for a minimum of six months and, therefore, the negative impact on mental health and overall quality of life (QoL) is larger.

Defining disease states in EGPA

EGPA is a poorly characterised rare disease, given the limited innovation and research in this space to date, resulting in a scarcity of literature to help inform the evolution of the disease. Consequently, extensive work was undertaken by AstraZeneca to deepen the understanding of the disease in support of this submission. This included systematic literature reviews, an advisory board with patients and extensive consultation with clinical experts.⁷⁻¹⁰ A separate workstream was also undertaken which included consultation with patients with EGPA through eight in-depth interviews and with clinical experts through four in-depth interviews, as part of defining the health state descriptions for the purpose of conducting a UK-specific vignette study.¹¹

All the gathered insights helped understand that, collectively, EGPA is best described by the four disease states outlined above, with patients broadly experiencing a relapsing and remitting disease course characterised by the occurrence of clinical signs and symptoms and different OCS doses required to control the disease. The definitions were validated during interviews with clinical experts.⁹ A visual depiction of the disease states is outlined in Figure 1.

Figure 1: EGPA disease states

	Remission (A)	Relapse (B)	Non-refractory (C)	Refractory (D)
Symptom burden				
Impact on quality of life				
Definition, as per economic model	BVAS = 0; AND OCS dose $\leq$ 4 mg/day	- Active vasculitis (BVAS $>$ 0); OR - Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR - Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting any of the following: - An increased dose of OCS therapy to $>$ 4 mg/day; OR - An increased dose or addition of immunosuppressive therapy; OR - Hospitalisation related to EGPA worsening	Stable OCS dose; OR Tapered OCS dose related to EGPA*	Persistent state over at least six months Not having achieved remission (BVAS = 0 and OCS dose $\leq$ 4 mg/day) at any time in the prior six months

NB: “Mild” symptom burden or impact on quality of life within the context of EGPA means that these patients always have some degree of symptom burden and impairment on quality of life despite being in the “best health state”, i.e. remission

#Significant worsening of symptoms which requires an escalation of treatment or hospitalisation

*Gradual reduction of OCS dose

Footnotes: Given data limitations, it was not possible to implement the refractory and non-refractory health states as individual health states. Therefore, these were modelled as sub-states within a ‘stable disease’ health state. The cost-effectiveness model included mutually exclusive alive disease states of remission, stable disease, and relapse.

Abbreviations: ACQ-6: asthma control questionnaire 6; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroids

How can refractory disease (referred to by NICE as “not under control”) be considered “stable”?

In EGPA, the term “not under control” in the refractory state reflects that a patient has not achieved remission (defined as Birmingham Vasculitis Activity Score [BVAS] = 0 and OCS dose ≤ 4 mg/day). This state is classified as “stable” as the patient has persistent disease activity and is, therefore, experiencing symptoms, but the clinical status of the patient has not significantly deteriorated to the point of requiring significant interventions (e.g. hospitalisation).



Difference between refractory disease (referred to by NICE as “not under control”) and a relapse (referred to by NICE as “flare up”)

In summary, the distinction between these two states is outlined below:

- Refractory disease indicates a failure to achieve remission at any time in the prior six months, but with no significant exacerbation or worsening of symptoms. Importantly, this state lasts for a minimum of six months and therefore the negative impact on overall QoL is larger.
- Relapse reflects an episode of significantly worsening symptoms requiring an escalation of treatment or hospitalisation.

b) In the CS Doc B (table 6) 25.7% of patients in the benralizumab arm had both refractory and relapsing disease at baseline.⁵ Please explain how patients can be in both disease states.

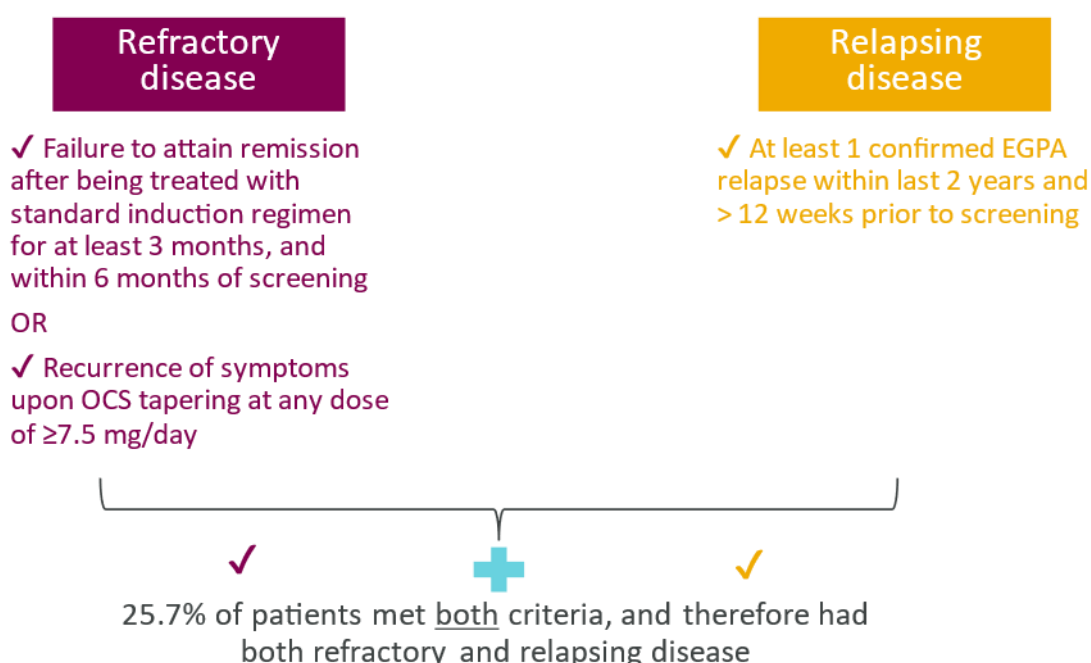
An inclusion criterion of MANDARA was for patients to have a history of refractory OR relapsing disease. Per the MANDARA inclusion criteria,

- Refractory disease was defined as failure to attain remission (defined as BVAS=0 and oral corticosteroid [OCS] dose ≤ 7.5 mg/day of prednisolone or equivalent), following standard induction regimen for at least 3 months and within 6 months prior to screening, or recurrence of symptoms upon OCS tapering at any dose of ≥ 7.5 mg/day prednisolone or equivalent
- Relapsing disease was defined as at least 1 confirmed EGPA relapse within last 2 years and >12 weeks prior to screening.

In line with these definitions, it was possible for patients to have both refractory and relapsing disease at baseline (Figure 2).

There is an important distinction between relapsing disease and a relapse. Patients were not included in MANDARA if they were experiencing a relapse at baseline. The health state being referred to in the economic model is a “relapse”. The definition of a relapse in the economic model is provided above in Figure 1.

Figure 2: Illustration of patients having both refractory and relapsing disease at baseline in MANDARA



Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; OCS: oral corticosteroids

A3: Transitions between disease states

In the file entitled 'AstraZeneca Data on File_CPRD Results 2024'¹² in the sheet labelled 'Refractory EGPA patients' there are tables detailing the numbers of patients

and their proportions in different disease states (remission, stable disease and relapse).

- a) Please clarify how patients were classified by disease state, how the information was calculated, and provide information on the duration of the disease states experienced (if available).

Classification of patients

In order to derive mutually exclusive health states for the economic model, the classification of patients in the Clinical Practice Research Datalink (CPRD) analysis was performed in a two-stage approach. Details are provided below and illustrated in Figure 3.

Step 1

- The primary clinical outcome (including a classification of disease state) was described in the incident cohort at the index date and during the follow-up period at every 6-month timepoint for 2 years (6, 12, 18, 24 months), with a 6-month look-back period at each timepoint, and then annually for years 3–5 (36, 48 and 60 months) with a 12-month look-back period at each timepoint.
- At each measurement, patients were categorised into one of three mutually exclusive disease states (remission, relapse, or stable disease) considering the previous observation period and assigned that disease state to the whole follow up period until the next timepoint.

The definitions used for each disease state is presented in Table 1.

Table 1: CPRD disease state definitions

Disease state	Definition used in analysis
Remission	In the observation period prior to each timepoint: - Systemic corticosteroids not used or all prescriptions with dose $\leq$ 4mg/day - No IS initiated (first ever prescription) - No new EGPA events - No hospitalisation for EGPA or EGPA events as primary diagnosis
Relapse	In the observation period prior to each timepoint: - New EGPA event OR - Hospitalised for EGPA or an EGPA event as primary diagnosis AND - Systemic corticosteroids: - Any initiation (first ever prescription) above 4 mg/day - Any re-initiation (gap >60days) above 4 mg/day - Any dose increased above 4 mg/day (i.e. any dose below 4mg/day with a posterior dose in the observation period above 4 mg/day OR all observations from previous period below or equal to 4 mg/day and first prescription of the period above 4 mg/day) OR IS:

	Initiation of IS (first ever prescription in the observation period)
Stable disease	Not in Remission and not in Relapse

Abbreviations: CPRD: Clinical Practice Research Datalink; EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressant; OCS: oral corticosteroids

Step 2

Refractory analysis at 6 months

An additional analysis of disease state at 6 months was performed to further stratify the disease status of people with 'stable disease' into non-refractory and refractory disease states (Table 2)

Table 2: CPRD stratified stable disease state definitions

Disease state	Definition used in analysis
Refractory	Not in Remission in current assessment period, plus not in Remission in the prior assessment period (at index date) i.e. over 6 months
Non-refractory	In stable disease (i.e. not in Remission and not in Relapse) and not Refractory

Footnote: Please note this stratification is performed within the stable disease state

Abbreviations: CPRD: Clinical Practice Research Datalink

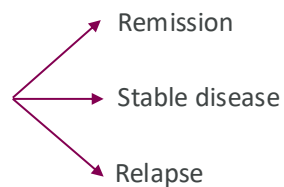
Importantly, transition probabilities for the economic model were not derived from CPRD – but from MANDARA instead. A comprehensive overview of the approach adopted to inform transition probabilities in the economic model, by treatment arm, is provided in Appendix 1.

Figure 3: Classification of patients in disease states from CPRD

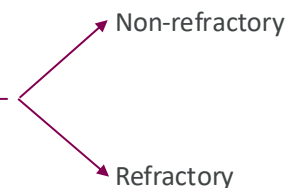
Step 1: Classification of patients into 3 mutually exclusive states

At each measurement

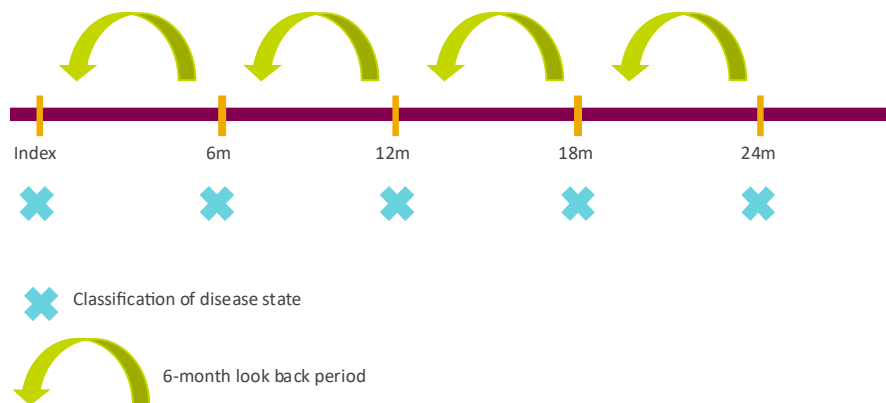
- Patients categorised into remission, stable disease or relapse based on the previous observation period
- Patients stay in that category till next observation period



Step 2: Stratifying 'stable' patients into "non-refractory" and "refractory" states



This stage of the analysis can only be performed from month 6 onwards, as refractory patients are defined as not having achieved remission in the last 6 months



Footnote: The illustration of Step 1 is shown only for the first 24 months (look-back period 6 months); for the subsequent years 3–5, the look-back period is 12 months

Duration of disease states experienced

The duration in a disease state cannot be calculated because no clear “stop/start” points can be defined for the state in the dataset. The analysis categorises patients in each state at the specified intervals which does not enable the accurate derivation of duration for each disease state. In conclusion, the CPRD dataset is not granular enough to calculate the duration of disease states.

- b) Please provide this information for patients in the benralizumab arm of MANDARA in addition.

Classification of patients

In order to derive transition probabilities for the economic model from MANDARA (comprehensive overview of the approach outlined in Appendix 1), a 2-stage process was adopted; firstly, patients were categorised in the 3 mutually exclusive states: remission, relapse and stable disease, followed by further stratification of the stable disease state into non-refractory and refractory states. Definitions are provided in Table 3 and Table 4.

Table 3: MANDARA disease state definitions used to derive transitions for the economic model

Disease state	Definition in MANDARA
Remission	- BVAS=0; AND - OCS dose $\leq$4 mg/day
Relapse	- Active vasculitis (BVAS >0); OR - Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR - Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting any of the following: - An increased dose of OCS therapy to >4 mg/day; OR - An increased dose or addition of IS therapy; OR - Hospitalisation related to EGPA worsening
Stable disease	Not in Remission and not in Relapse

Abbreviations: ACQ-6: asthma control questionnaire 6; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis

Table 4: MANDARA stratified stable disease state definitions

Disease state	Definition in MANDARA
Refractory	Failure to achieve Remission (defined as BVAS=0 and OCS dose $\leq$ 4 mg/day) for the preceding 6 months
Non-refractory	In stable disease (i.e. not in Remission and not in Relapse) and not Refractory - Stable OCS dose; OR - Tapered OCS dose related to EGPA

Footnote: Please note this stratification is performed within the stable disease state.

Given data limitations, it was not possible to implement the refractory and non-refractory health states as individual health states. Therefore, these were modelled as sub-states within a ‘stable disease’ health state. The cost-effectiveness model included mutually exclusive alive disease states of remission, stable disease, and relapse.

Duration of disease states experienced

An analysis that explored the average time patients spent in each disease state is presented in Table 5. The analysis was conducted by summing the total time patients spent in each disease state (across the cohort) divided by the number of patients who entered the disease state.

Table 5: Average duration spent in each disease state

Disease state	Number of patients (N)	Average time spent in state (months) ^a
Remission	■	■
Stable disease	■	■
Relapse	■	■

Footnotes: ^a The sum of months will not equal 12 as the analysis excludes patients who do not enter the health state at any point. Average time spent in health state does not consider patients who did not reach the health state.

Source: Analysis was based on individual patient data (IPD) from MANDARA

A4. Standard of care across trial countries

In the CS Doc B, the patients in MANDARA are drawn from North America, Japan and the 'rest of the world'.⁵ The primary study publication¹³ provides a breakdown of the randomised patients into individual countries. Please report any differences in the use (and any tapering regimen) of oral corticosteroids (OCS) and immunosuppressants (IS) by country.

The baseline average daily OCS dose and IS usage data by country are provided below.

Based on these data, standard of care across the MANDARA trial sites is comparable and generalisable to the UK.

OCS dose and tapering by country

The baseline average daily OCS dose across the different countries is shown in Table 6.

The baseline average daily OCS dose for patients in the UK within MANDARA was comparable to the weighted average of countries (■ mg versus 11.0 mg, respectively). Small variations in OCS usage by country are expected owing to differences in healthcare systems and prescribing practices.

Of note, the baseline average daily OCS dose for patients in Belgium was notably higher than other countries (■ mg versus 11.0 mg, respectively); however, interpretations of these results should be taken with caution owing to the small sample size (■).

Tapering of OCS is evidenced in the downward trend of OCS usage for all countries starting from Weeks 5–8. The MANDARA protocol allowed OCS tapering from Week 4 (please see Appendix H in the MANDARA protocol)¹⁴ – tapering of OCS was subject to investigator discretion at different sites which explains the minor fluctuations in OCS dosage seen in Figure 4.

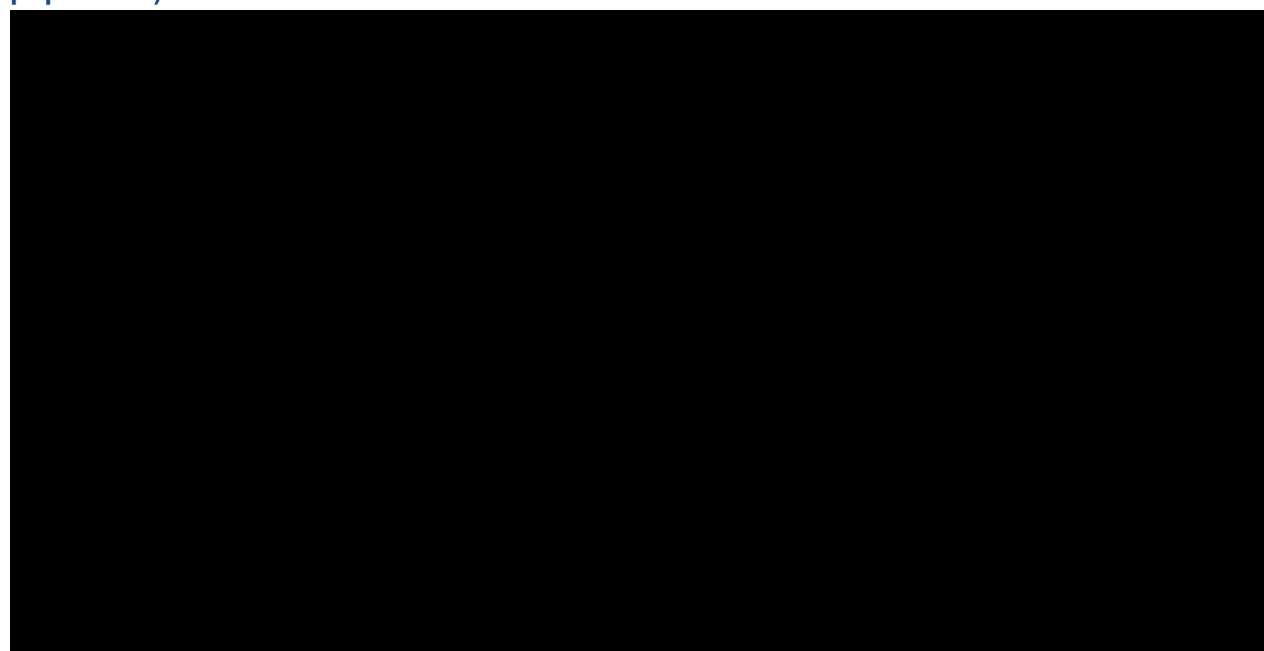
Table 6: Baseline average daily OCS dose by country (full MANDARA population)

	Belgium (N=■)	Canada (N=■)	France (N=■)	Germany (N=■)	Israel (N=■)	Italy (N=■)	Japan (N=■)	UK (N=■)	USA (N=■)
Baseline average daily OCS dose (mg)	■	■	■	■	■	■	■	■	■

Footnote: OCS was administered as prednisolone; average is mean

Abbreviations: OCS: oral corticosteroids

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

Figure 4: OCS usage by country across the 52-week trial period (full MANDARA population)

Abbreviations: OCS: oral corticosteroids

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

IS usage by country

The baseline proportion of all patients on an IS therapy by country is shown in Table 7.

The proportion of patients on IS therapy at baseline in the UK within MANDARA was comparable to the weighted average of countries (■% versus ■%, respectively).

The proportion of patients on IS therapy at baseline ranged between ■ and ■% in most countries. Higher percentages of patients on IS were seen in Belgium and Germany versus other countries (~■% and ~■%, respectively) likely owing to variation in prescribing practices of healthcare professionals in the two countries.

Table 7: Baseline proportion of IS use by country (full MANDARA population)

	Belgium (N=■)	Canada (N=■)	France (N=■)	Germany (N=■)	Israel (N=■)	Italy (N=■)	Japan (N=■)	UK (N=■)	USA (N=■)
Baseline proportion of patients on IS (%)	■	■	■	■	■	■	■	■	■

Abbreviations: IS: immunosuppressants

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

A5. UK trial participants

The EAG note that 18 participants were drawn from the UK.¹³ These were centred at four trial sites (Cambridge, Leicester, London, Portsmouth). To understand how treatment differs between hospitals in the UK, please replicate the information required for question A3 for UK sites.

AstraZeneca thank the EAG for clarifying that the information should be replicated from question A4, rather than A3.

The average daily OCS dose and IS usage data by trial site in the UK are provided below.

OCS dose and tapering by UK site

The baseline average daily OCS dose across the different UK trial sites is shown in Table 8.

The baseline average daily OCS dose between sites in the UK within MANDARA ranged between ■ and ■ mg; small degrees of variation are expected owing to different prescribing practices across treatment sites.

The MANDARA protocol¹⁴ allowed OCS tapering from week 4 onwards, in line with UK clinical practice, as validated by clinical experts.⁹ However, the actual tapering of OCS is subject to investigator discretion at different sites which explains the fluctuation in OCS dosage observed in Figure 5.

Table 8: Baseline average daily OCS dose by UK site (full MANDARA population)

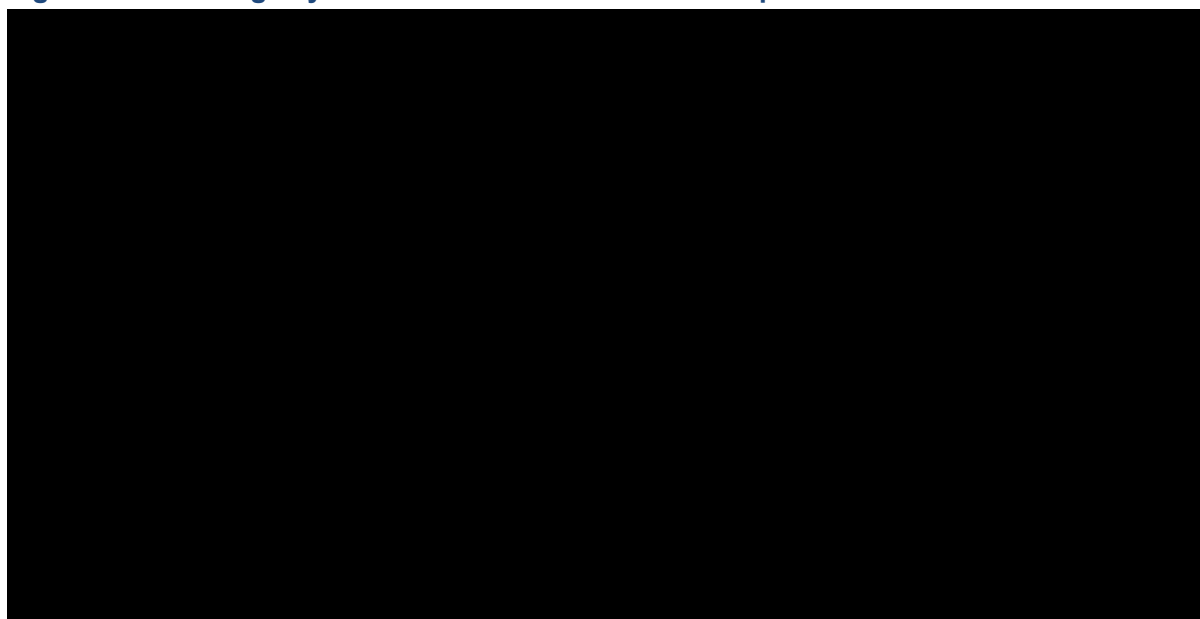
	London (N=■)	Cambridge (N=■)	Leicestershire (N=■)	Portsmouth (N=■)
Baseline average daily dose (mg)	■	■	■	■

Footnote: OCS is administered as prednisolone

Abbreviations: OCS: oral corticosteroids

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

Figure 5: OCS usage by UK trial site across the 52-week period



Abbreviations: OCS: oral corticosteroids

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

IS usage by UK site

The baseline proportion of all patients on an IS therapy by UK site is shown in Table 9.

The proportion of patients on IS therapy at baseline between sites in the UK within MANDARA ranged between █% and █%; small degrees of variation are expected (and confirmed by clinical experts)^{9, 16} owing to different prescribing practices across treatment sites. Furthermore, no meaningful conclusions can be drawn from these observations owing to small sample sizes.

Table 9: Baseline proportion of IS use by UK trial site

	London (N=█)	Cambridge (N=█)	Leicestershire (N=█)	Portsmouth (N=█)
Baseline proportion of patients on IS (%)	█	█	█	█

Abbreviations: IS: immunosuppressants

Source: AstraZeneca. Data on File. MANDARA Baseline OCS and IS Dose¹⁵

A6. Clinical experts

In CS Appendices (D.1.10),¹ four clinical experts provided insight into the ranking of treatment effect modifiers. Please detail how the clinical experts were recruited/screened, were there any conflicts of interest, whether they were UK-based, and what level of expertise in EGPA they have. Are these clinical experts different to those referred to in the CS Doc B in the protocol CSR Data folder (Data on File 3)?⁹

The four experts consulted to rank treatment effect modifiers are global specialists in the management and research pertaining to EGPA (determined by clinical lead status, publication history and guideline committee involvement), all of whom participated in the MANDARA trial as investigators and/or experts. Further detail is provided about the four experts below:

- One expert is UK-based with expertise in vasculitis, lupus and rare renal disease;
- Two experts are based in the United States (US) and are specialists in asthma, vasculitis, eosinophilic lung diseases and EGPA;
- One expert is based in Canada with a specialist interest in vasculitis.

There was overlap with one clinical expert in both exercises (insights provided by four experts on the ranking of treatment effect modifiers and feedback elicited from three clinical experts, referenced in Data on File 3).⁹

A7. Stopping criteria

In the open label extension trial,¹⁷ [REDACTED] patients experienced adverse events and discontinued with further treatment. Please detail what stopping criteria is proposed for benralizumab in this population.

As AEs (details of AEs below) were deemed to be unrelated to long-term treatment with benralizumab, no stopping criteria pertaining to AEs are proposed.

Note – a stopping criteria in the form of a response assessment was conducted at 52 weeks in the economic model; consistent with the recommended use of benralizumab in severe asthma and in line with the anticipated use of benralizumab in EGPA in UK clinical practice.^{9, 18}

Responders (defined as BVAS=0 and an OCS dose $\leq$ 4 mg/day) will continue to receive benralizumab and non-responders will discontinue treatment with benralizumab and receive standard of care (SoC).

A total of [REDACTED] patients entered the MANDARA open label extension (OLE); [REDACTED] patients continued treatment with benralizumab and [REDACTED] switched from mepolizumab to benralizumab. In the OLE, [REDACTED] patients experienced adverse events and discontinued further treatment. Out of these [REDACTED] patients, [REDACTED] receiving benralizumab and [REDACTED] receiving mepolizumab in the double-blind (DB) period of MANDARA.

Regarding the [REDACTED] on benralizumab during the DB study

- [REDACTED]
- [REDACTED]

[REDACTED] adverse events required treatment and the adverse events were not resolved.

Regarding the [REDACTED] on mepolizumab during the DB study

[REDACTED]

A8. OCS dosage

Priority question: Please detail how (a) ‘maintenance doses’ of OCS and b) ‘courses’ of OCS vary by disease state (remission, relapsed, refractory, non-refractory) in the MANDARA trial. Please disaggregate this information by the disease states and patient characteristics (such as asthma severity).

‘Maintenance doses’ of OCS vs ‘courses’ of OCS

Overall OCS doses from MANDARA have been analysed by disease state as an aggregate based on prescription data. The data lack granularity to disaggregate the OCS dose into ‘maintenance doses’ and ‘courses’ of OCS, as the prescriptions did not distinguish whether the OCS doses are for ‘maintenance’ or acute treatment. However, the ‘courses’ of OCS were included in the aggregate OCS dose by disease state. Consistent with that, relapse was associated with a higher daily OCS dose because those patients are expected to be prescribed additional OCS courses when treatment escalation is required.

The OCS-sparing treatment goal applies to total exposure, i.e. maintenance OCS and OCS ‘courses’. Additionally, OCS-related AEs occur based on cumulative dose (regardless of whether the OCS was used as a maintenance or a ‘course’). It is, therefore, appropriate to consider a reduction in the overall OCS use.

OCS doses from MANDARA, disaggregated by disease states

The mean daily OCS dose stratified by disease state for patients in the benralizumab arm of MANDARA is presented in Table 10.

For the purpose of the economic model, OCS doses were informed by CPRD, as these are most representative of UK clinical practice.

Table 10: Mean daily OCS dose by disease state, from MANDARA

Disease state	Mean OCS (mg/day)	SE
Remission	■	■
Non-refractory	■	■
Refractory	■	■
Relapse	■	■

Footnotes: The analysis is based only on data from month 6 onwards, based on the definition of patients with refractory disease being that they did not achieve remission over the last 6 months. Additionally, please note in the economic model, OCS doses are informed by a CPRD analysis and are captured for the 3 health states: remission, stable disease, and relapse.

Abbreviations: CPRD: Clinical Practice Research Datalink; mg: milligram; OCS: oral corticosteroids; SE: standard error

Source: Analysis was based on IPD from MANDARA

OCS doses from MANDARA, disaggregated by patient characteristics

The question requests the OCS doses to be disaggregated by asthma severity; however, this can be defined in many ways; for example, controlled vs uncontrolled asthma can be in terms of

asthma control questionnaire 6 (ACQ-6), a measure already included within the definition of relapse. Therefore, it would not be possible to further stratify the OCS dose by disease state and a patient reported outcome (PRO) such as ACQ-6. Additionally, as discussed at the clarification question call, an increase in ACQ-6 is only one of the criteria for a relapse. However, the sample size from which to perform the disaggregation was severely limited after isolating patients who (i) had a relapse but (ii) did not have an increase in ACQ-6. Therefore, meaningful conclusions could no longer be drawn from the results.

Instead, mean daily OCS doses from MANDARA, disaggregated by age and vascular damage index (VDI) in the benralizumab arm are provided below. Table 11 shows that OCS doses are consistent by disease state, irrespective of stratification by patient characteristics.

Table 11: Mean daily OCS dose by age and VDI, from MANDARA

Stratification	Disease state	Mean OCS (mg/day)	SE
Age ≤65 years	Remission	■	■
	Non-refractory	■	■
	Refractory	■	■
	Relapse	■	■
Age >65 years	Remission	■	■
	Non-refractory	■	■
	Refractory	■	■
	Relapse	■	■
VDI <5	Remission	■	■
	Non-refractory	■	■
	Refractory	■	■
	Relapse	■	■
VDI ≥5	Remission	■	■
	Non-refractory	■	■
	Refractory	■	■
	Relapse	■	■

Abbreviations: VDI: Vascular damage index; OCS: oral corticosteroids; SE: standard error

Source: Analysis was based on IPD from MANDARA

A9. Patients with severe disease excluded from MANDARA

The NICE scope details the population as ‘adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy’.¹⁹ In the MANDARA trial, the inclusion criteria excludes patients which have previously had rituximab within 6

months prior to screening, oral cyclophosphamide within 2 weeks prior to baseline, intravenous cyclophosphamide within 3 weeks prior to baseline and recent or ongoing organ-threatening or life-threatening EGPA.²⁰ Please explain the rationale for excluding patients with recent severe disease (especially when the disease course may be very heterogenous).

MANDARA was designed to be a head-to-head, non-inferiority study to mepolizumab. At the time of planning, mepolizumab was anticipated to be the standard of care for when benralizumab would be entering clinical practice and evaluated by HTA bodies.

Consequently, the study population of MANDARA was aligned as closely as possible to MIRRA. As per the inclusion criteria of the MIRRA study, patients with organ threatening or life-threatening EGPA (i.e. severe EGPA) within 3 months prior to screening and through randomisation were also excluded from the MANDARA study.

A10. Immunogenicity

During the clinical expert interviews (Data on File 3),⁹ it was agreed that the treatment effect of benralizumab [REDACTED]. The EAG noted that 9% of the MANDARA safety population presented with anti-drug antibodies in response to benralizumab, one of which was neutralising.¹³ Is there an increased risk of immunogenicity, and potential for a reduction in efficacy in patients in the long-term (i.e., >1 year) receiving the higher dose (Q4W) of benralizumab than those receiving the lower dose (Q8W), and if so, has this been taken into account (particularly for patients that have been exposed to biologics before)? The EAG are aware this data may not yet be available for this population, but please provide any supporting information from the severe asthma population.

Risk of immunogenicity/potential for reduction in efficacy, based on dose frequency

Data exploring the potential risk of immunogenicity with the higher dose (every 4 weeks [Q4W]) of benralizumab in an EGPA population is not available. However, data in a severe asthma population are available; the results and conclusions from the BORA study²¹ (NCT02258542; phase 3 extension study evaluating the safety and efficacy of benralizumab in patients with severe eosinophilic asthma) are outlined below:

- ADA responses were generally similar between patients in the every 8 weeks (Q8W) and the every 4 weeks (Q4W) group.²²
- Benralizumab serum concentrations in ADA-positive patients remained stable during BORA, and ADA-positive patients exhibited near complete depletion of EOS over time.

In summary, based on BORA, there was no evidence that different dose regimens (Q8W vs Q4W) impacted ADA incidence or that ADA-positive status had an effect on safety, efficacy, or exposure of benralizumab over time.

In addition, based on a recent systematic literature review (SLR) and meta-analysis of asthma biologics exploring the incidence of ADAs and their impact on reported clinical outcomes showed that the incidence of neutralising antibodies was higher in the Q8W arm (8.17%) vs every Q4W (5.81%).²³ The SLR also highlighted that only 2.9% of individuals in the included studies developed ADAs over the study follow-up period and that longer dosing intervals were associated with higher ADA development.²³

Risk of immunogenicity/potential for reduction in efficacy, based on prior exposure to biologics

During the MANDARA OLE, ADA levels were assessed in patients randomised to receive mepolizumab in the DB period with the hypothesis of understanding the ADA rate in patients who switched treatment from mepolizumab to benralizumab. No meaningful differences in ADA rates was observed in this population indicating that prior exposure to a previous biologic treatment does not result in elevated immunogenicity risk and greater incidence and prevalence of ADAs.²⁴

Based on all the evidence outlined above, the risk of immunogenicity or subsequent potential for reduction in efficacy of benralizumab does not increase with a higher frequency dose or prior exposure to biologics. Consequently, this was not reflected in the economic model.

A11. Female patients by age

Please provide the proportion of female patients by age group in 5-year intervals for (a) MANDARA and; (b) the CPRD registry (if available) to determine the number of trial participants at higher risk from fertility problems/osteoporosis arising from OCS adverse events.

Table 12 presents the proportions of female patients by age group in 5-year intervals for MANDARA and CPRD.

Of note, both males and females are at risk of developing osteoporosis arising from OCS AEs; females are at an even higher risk.²⁵

Table 12: Proportion of female patients by age group from MANDARA and CPRD

Age group, years	Frequency	
	MANDARA (N=140)	CPRD (N=486)
0–15	■	■
16–20	■■■	■
20–25	■■■	■
26–30	■■■	■■■

31–35	■	■
36–40	■	■
41–45	■	■
46–50	■	■
51–55	■	■
56–60	■	■
61–65	■	■
66–70	■	■
71–75	■	■
75–80	■	■
81–85	■	■
86–90	■	■
90+	■	■

Abbreviations: CPRD: Clinical Practice Research Datalink; NA: not applicable

Source: Analysis was based on IPD from MANDARA and CPRD dataset

A12. MANDARA Open Label Extension (OLE) baseline characteristics

The MANDARA interim results (AstraZeneca Data on File_MANDARA OLE Interim Results)²⁶ [REDACTED]

[REDACTED]. Is this explained by switching drugs, due to some patients not enrolling in the open-label extension or another reason? Please provide the baseline characteristics of patients entering the MANDARA open-label extension, if available.

During the OLE, patients switching from mepolizumab to benralizumab took their first dose of benralizumab at Week 52. The subsequent steep reduction in blood EOS count as well as reduction in OCS usage at Week 56 is owing to the switching of interventions and their different mechanisms of action and resulting EOS depletion. Additionally, baseline characteristics of patients in the OLE period of MANDARA were closely aligned to those in the DB period and are, therefore, unlikely to have had an impact on the observations at Week 56. Further detail is provided below.

Impact of benralizumab, compared to mepolizumab, on blood EOS count and OCS usage

Blood EOS count

Benralizumab uniquely binds to IL-5 α , blocking all pathways to eosinophil activation resulting in rapid and near complete depletion of sputum and blood eosinophils.²⁷ Mepolizumab, however, selectively targets the activity of the IL-5 cytokine, without affecting the remaining cytokine network involved in eosinophil activation; as such, mepolizumab induces a reduction in sputum

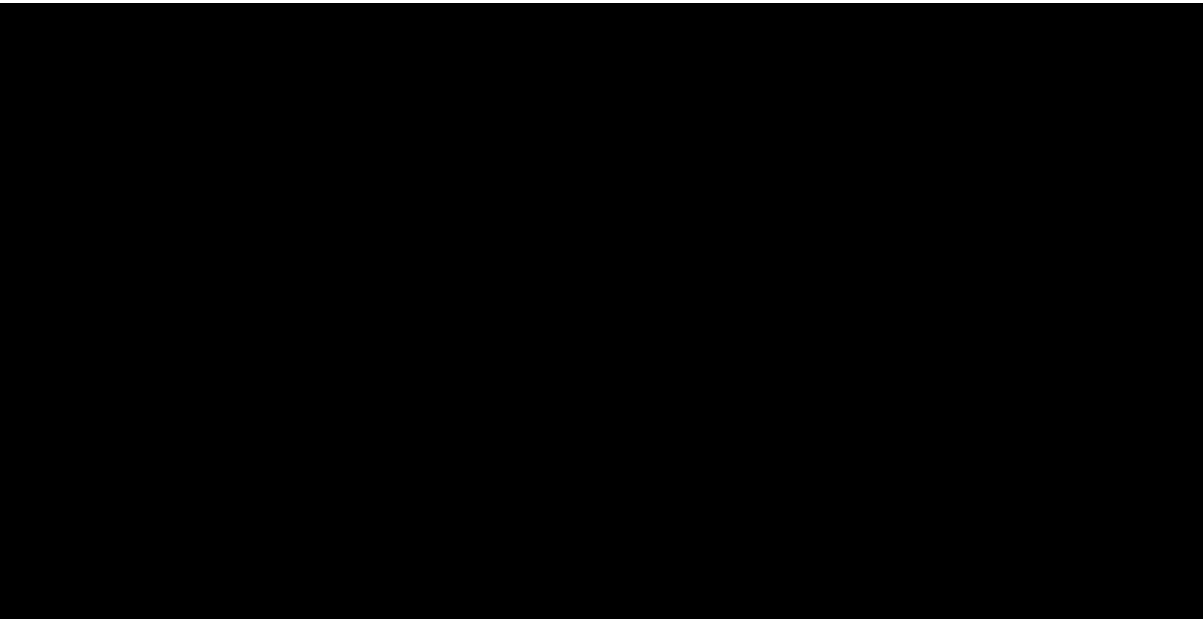
and blood eosinophils to a lesser extent than benralizumab. This is further supported by the MEX study which shows that treatment with mepolizumab in severe refractory eosinophilic asthma resulted in continued exacerbations, suggesting it was less effective at EOS depletion.²⁸ Importantly, benralizumab achieves this near-depletion of blood EOS as rapidly as within a week, as demonstrated by the % change difference in eosinophils detailed in Table 13 and illustrated in Figure 6.

Table 13: EOS counts across the 52-week trial period of MANDARA

Time point	Statistic	Benralizumab 30 mg (N=70)		Mepolizumab 300 mg (N=70)	
		Absolute EOS count (cells/µl)	% change from baseline	Absolute EOS count (cells/µl)	% change from baseline
Baseline ^a	N	70	-	70	-
	Mean (SD)	306.0 (225.0)	-	384.9 (563.6)	-
Week 1	N	█	█	█	█
	Mean (SD)	██████	██████	██████	██████
Week 52	N	█	█	█	█
	Mean (SD)	██████	██████	██████	██████

Footnotes: ^a Baseline is defined as the last non-missing measurement on or prior to the date of randomisation.
Abbreviations: BVAS: Birmingham Vasculitis Activity Score; EOS: eosinophil; N: number of patients in treatment group; SD: standard deviation
Source: Wechsler M, et al. New England Journal of Medicine, 2024;¹³ AstraZeneca MANDARA CSR.²⁹

Figure 6: Absolute EOS count, least squares mean change from baseline by timepoint, line plot (full analysis set)



Abbreviations: EOS: eosinophil; mg: miligram
Source: AstraZeneca MANDARA CSR.²⁹

OCS usage

In the DB period of MANDARA, benralizumab was consistently associated with a greater reduction in OCS usage compared to mepolizumab (Table 14) – which explains why switching interventions leads to the reduction in OCS usage observed at Week 56.

Table 14: Proportion of patients with reduction from baseline in average daily dose of OCS during Weeks 48 through 52 (full analysis set)

	Treatment group	Number (%) of patients with reduction	Adjusted rate (%) ^a	Comparison between groups		
				Difference in rates (%) ^a	95% CI	p value ^b
≥50% OCS reduction	Benralizumab 30 mg (N=70)	59 (84.3)	84.7	10.8	-2.3, 23.8	0.1047
	Mepolizumab 300 mg (N=70)	52 (74.3)	73.9	-	-	-
100% OCS reduction	Benralizumab 30 mg (N=70)	29 (41.4)	41.4	15.7	0.7, 30.7	0.0406
	Mepolizumab 300 mg (N=70)	18 (25.7)	25.8	-	-	-
OCS dose ≤4 mg/day	Benralizumab 30 mg (N=70)	48 (68.6)	68.9	-0.7	-15.6, 14.2	0.9283
	Mepolizumab 300 mg (N=70)	49 (70.0)	69.6	-	-	-
OCS dose =0 mg/day	Benralizumab 30 mg (N=70)	██████	NR	NR	NR	NR
	Mepolizumab 300 mg (N=70)	██████	NR	NR	NR	NR

Footnotes: ^a The rates and the difference (benralizumab – mepolizumab) were estimated using marginal standardisation method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS and region. Baseline was defined as the last measurement on or prior to the date of randomisation.

^b 2-sided p value. p values were not multiplicity adjusted.

If patients withdrew early from the study prior to Week 52, the daily dose of OCS for the last 28 days was used to derive the average daily dose during Week 48 through 52. Patients who withdrew from investigational product before Week 48 were considered non-responders for % reduction in OCS.

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; N: number of patients in treatment group; OCS: oral corticosteroids

Source: Wechsler M, *et al.* New England Journal of Medicine, 2024;¹³ AstraZeneca MANDARA CSR, 2023²⁹

OLE baseline characteristics

Table 15 presents the baseline characteristics of patients in the DB and OLE periods of MANDARA. The only change to the dataset between the DB period and the OLE period was the loss of 12 patients. This small number of patients is unlikely to have had an impact on the steep reduction in blood EOS count or OCS usage observed.

Table 15: MANDARA DB and OLE baseline characteristics

Characteristic	Benralizumab DB (N=70)	Benralizumab OLE (N=66)	Mepolizumab DB (N=70)	Mepolizumab switched to benralizumab for OLE (N=62)
Age, years				
Mean (SD)	52.0 (13.9)	████████	52.7 (14.4)	████████
Median (min, max)	55.0 (20, 76)	████████	55.0 (19, 79)	████████
Sex, n (%)				
Female	45 (64.3)	████████	39 (55.7)	████████
Region, n (%)				
North America	16 (22.9)	████████	16 (22.9)	████████
Japan	4 (5.7)	██████	4 (5.7)	██████
Rest of World	50 (71.4)	████████	50 (71.4)	████████
EGPA disease type, n (%)				
Relapsing disease	45 (64.3)	████████	48 (68.6)	████████
Refractory disease	42 (60.0)	████████	42 (60.0)	████████
Relapsing and refractory disease	18 (25.7)	████████	20 (28.6)	████████
EOS count,^a cells/μL				
Mean (SD)	306.0 (225.0)	████████	384.9 (563.6)	████████
Median (min, max)	240.0 (30, 920)	████████	225.0 (0, 3830)	████████
BVAS^b				
Mean (SD), mg/day	2.3 (3.5)	████████	1.9 (2.9)	████████
>0, n (%)	34 (48.6)	████████	33 (47.1)	████████
OCS use^c				
Mean (SD), mg/day	11.1 (4.6)	████████	11.0 (5.9)	████████
Median (mix, max)	10.0 (5.0, 30.0)	████████	10.0 (7.5, 40.0)	████████
≥12 mg/day, n (%)	18 (25.7)	████████	14 (20.0)	████████
IS therapy use at baseline, n (%)				
	26 (37.1)	████████	24 (34.3)	████████
VDI score^d				
Mean (SD)	4.0 (1.8)	████████	4.0 (1.8)	████████
≥5, n (%)	23 (32.9)	████████	21 (30.0)	████████
Time since diagnosis of EGPA, years				
Mean (SD)	5.4 (5.4)	████████	4.9 (5.9)	████████
Median (min, max)	██ (0.6, 24.0)	████████	██ (0.1, 38.0)	████████

Footnotes: ^a Patients entered MANDARA on stable OCS with or without IS, as per the inclusion criteria, and therefore, their EOSs were being suppressed. As a result, the baseline eosinophil counts for patients in MANDARA were lower than would be expected for patients with EGPA who are not receiving treatment

^b The BVAS ranges from 0 to 59, with higher scores indicating more severe disease

^c The dose of oral glucocorticoid was calculated as the daily dose of prednisone or prednisolone, regardless of the reason for administration

^d Scores on the VDI range from 0 to 64, with higher scores indicating greater organ damage

Abbreviations: BVAS: Birmingham Vasculitis Activity Score; DB: double-blind; EGPA: Eosinophilic granulomatosis with polyangiitis; max: maximum; mg: milligram; min: minimum; N: number of patients in treatment group; OCS: oral corticosteroids; OLE: open-label extension; SD: standard deviation; VDI: Vasculitis Damage Index

Source: AstraZeneca MANDARA CSR;²⁹ AstraZeneca. Data on File. MANDARA OLE baseline characteristics³⁰

A13. Patients experiencing lack of efficacy during the MANDARA OLE

The EAG noted that [REDACTED] (AstraZeneca Data on File_MANDARA OLE Interim Results),²⁶ did these patients achieve remission with either benralizumab or mepolizumab in the MANADARA double blind study?

AstraZeneca thank the EAG for confirming that the [REDACTED] patients mentioned in this question was a typo and this should be [REDACTED].

Of the [REDACTED] patients who discontinued treatment owing to lack of efficacy, [REDACTED] were receiving benralizumab and [REDACTED] were receiving mepolizumab in the DB period of MANDARA.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Further detail about the [REDACTED] remaining patients who discontinued treatment due to lack of efficacy is presented in Table 16.

Table 16: Detail about patients who discontinued treatment due to lack of efficacy

Receiving benralizumab in DB period	Receiving mepolizumab in DB period
[REDACTED]	[REDACTED]
	[REDACTED]
	[REDACTED]

Footnote: Primary endpoint defined as remission (defined as BVAS=0 and OCS dose ≤4 mg/day) at both weeks 36 and 48; ^a Patient discontinued mepolizumab at end of DB period of MANDARA and switched to benralizumab
Abbreviations: BVAS: Birmingham Vasculitis Activity Score; DB: double-blind

In response to the EAG's additional query shared via email of "Do these [REDACTED] patients form [REDACTED] [REDACTED] patients who were ADA-positive?" – no, these were [REDACTED] different patients.

A14. Inputs used in the Bucher ITC

- The Bucher ITC results are presented in Doc B. section B.2.9.2. ⁵ Please cross-reference the precise source for the ORs and RRs reported in Table 18. For estimates from the MANDARA trial, please cross-reference where in the CS these data were reported.

The Bucher indirect treatment comparison (ITC) inputs are summarised in Table 17. MANDARA estimates used in the Bucher ITC were derived for benralizumab vs placebo using models fit to

individual patient data for the full analysis set (N=140). MIRRA values were reported in Wechsler et al. 2017 for mepolizumab vs placebo for the intention-to-treat population (N=136).³¹ Reported MIRRA values were inverted prior to being used in the Bucher ITC to derive the estimates for placebo vs mepolizumab.

Table 17: Bucher ITC inputs from MANDARA and MIRRA

Outcome	Bucher ITC Inputs		Bucher ITC Results (Benra vs Pbo)
	MANDARA ^a (Benra vs Mepo)	MIRRA ^b (Mepo vs Pbo)	
Binary Outcomes	OR (95% CI)	OR (95% CI)	OR (95% CI)
Proportion of patients in remission at both Week 36 and Week 48 (main remission definition) ^c	██████████ ██████████	██████████ ██████████	██████████ ██████████
Rate Outcomes	RR (95% CI)	RR (95% CI)	RR (95% CI)
Annualised relapse rate	██████████ ██████████	██████████ ██████████	██████████ ██████████

Footnotes: ^a MANDARA estimates were derived for benralizumab vs placebo using models fit to individual patient data for the full analysis set (N=140).

^b MIRRA values were reported in Wechsler et al. 2017 for mepolizumab vs placebo using the intention-to-treat population (N=136). Reported values were inverted prior to being used in the Bucher ITC to derive the estimates for placebo vs mepolizumab.

^cMain remission is defined as a BVAS of 0 plus OCS dose of prednisolone/prednisone ≤4 mg/day.

Abbreviations: Benra: benralizumab; CI: confidence interval; ITC: indirect treatment comparison; Mepo: mepolizumab; OR: odds ratio; Pbo: placebo; RR: rate ratio.

Source: AstraZeneca. Data on File. MANDARA Bucher ITC³²

- b) Please provide the inputs (OR/HR and SEs/95% CIs) from the MANDARA and MIRRA trials used in the Bucher ITCs reported in Table 16, Appendix D¹ so that the EAG can check the reproducibility of these analyses.

MANDARA estimates used in the Bucher ITC were derived for benralizumab vs placebo using models fit to individual patient data for the full analysis set (N=140). MIRRA values were reported in Wechsler et al. 2017 for mepolizumab vs placebo for the intention-to-treat population (N=136).³¹ Reported MIRRA values were inverted prior to being used in the Bucher ITC to derive the estimates for placebo vs mepolizumab. These inputs are presented in Table 18.

Table 18: Bucher ITC inputs from MANDARA and MIRRA (additional outcomes)

Outcome	Bucher ITC Inputs		Bucher ITC Results (Benra vs Pbo)
	MANDARA ^a (Benra vs Mepo)	MIRRA ^b (Mepo vs Pbo)	
Binary Outcomes	OR (95% CI)	OR (95% CI)	OR (95% CI)
Proportion of participants in remission at both week 36 and week 48 (supportive remission definition) ^c			
Proportion of participants who achieved remission within the first 24 weeks and stayed in remission until 52 weeks (main remission definition) ^d			
Proportion of participants who achieved remission within the first 24 weeks and stayed in remission until 52 weeks (supportive remission definition)			
Ordinal Outcomes	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total accrued duration of remission over a 52-week period (main remission definition) ^{d,e}			
Total accrued duration of remission over a 52-week period (supportive remission definition) ^{c,e}			
Average daily OCS dose during the last four weeks of the study (weeks 48 through 52) ^f			
Time to Event Outcomes	HR (95% CI)	HR (95% CI)	HR (95% CI)
Time to first EGPA Relapse			

Footnotes: ^a MANDARA estimates were derived for benralizumab vs placebo using models fit to individual patient data for the full analysis set (N=140).

^b MIRRA values were reported in Wechsler et al. 2017 for mepolizumab vs placebo using the intention-to-treat population (N=136). Reported values were inverted prior to being used in the Bucher ITC to derive the estimates for placebo vs mepolizumab.

^c Supportive remission is defined as a BVAS of 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day

^d Main remission is defined as a BVAS of 0 plus OCS dose of prednisolone/prednisone ≤4 mg/day.

^e The categories for total accrued duration of remission over a 52-week period are: 0 weeks, > 0 to 12 weeks, 12 to < 24 weeks, 24 to < 36 weeks, and ≥ 36 weeks.

^f The categories for average daily OCS dose during the last four weeks of the study (weeks 48 through 52) are: 0 mg, > 0 to ≤ 4 mg, > 4 to ≤ 7.5 mg, and > 7.5 mg.

Main remission is defined as a BVAS of 0 plus OCS dose of prednisolone/prednisone ≤4 mg/day.

Abbreviations: Benra: benralizumab; CI: confidence interval; ITC: indirect treatment comparison; Mepo: mepolizumab; OR: odds ratio; Pbo: placebo; RR: rate ratio.

Source: AstraZeneca. Data on File. MANDARA Bucher ITC³²

A15. Immunosuppressant therapy

In the MANDARA trial the EAG noted that the study inclusion criteria immunosuppressant dose reductions were permitted during the trial for safety reasons, and a dose increase, or an addition of immunosuppressive therapy could occur in response to a relapse.²⁰ The number of patients in the trial receiving immunosuppressants is presented at baseline in table 6 in Doc B section B.2.3.2.⁵ Please provide the number of patients over the double blind period that continued to receive a stable dose, those that changed their dosage, and the number of patients that were initiated on immunosuppressants.

Table 19 presents the number of patients on IS at baseline, patients over the DB period who continued to receive a stable dose, patients who changed their dosage (increased or decreased), and the number of patients who were initiated on IS.

Table 19: Data on IS therapy from MANDARA at baseline

	Benralizumab 30 mg (N=70)	Mepolizumab 300mg (N=70)	Total (N=140)
Number of patients on IS at baseline	■	■	■
Number (%) of patients with stable dose of IS ^{a,b}	■■■■■	■■■■■	■■■■■
Number (%) of patients who stopped or lowered dose of IS ^b	■■■■■	■■■■■	■■■■■
Number (%) of patients who increased dose of IS ^b	■	■	■
Number (%) of patients who initiated IS ^c	■■■■■	■	■■■■■

Footnotes: Baseline is defined as the last measurement on or prior to the date of randomization.

Only IS that are for EGPA indication are included.

^a included subject who has stable dose of IS throughout the DB period.

^b percentage is based on number of subjects on IS at baseline.

^c percentage is based on number of subjects in treatment group.

If subjects stop or lower dose, and increase dose of IS during DB period, they will only be counted in 'increase dose of IS'.

If subjects stop or lower dose, and initiate new IS during DB period, they will only be counted in 'initiate IS'.

Abbreviations: DB: double-blind; EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressant

Source: AstraZeneca. Data on File. MANDARA IS Dose Change From Baseline³³

Section B: Clarification on cost-effectiveness data

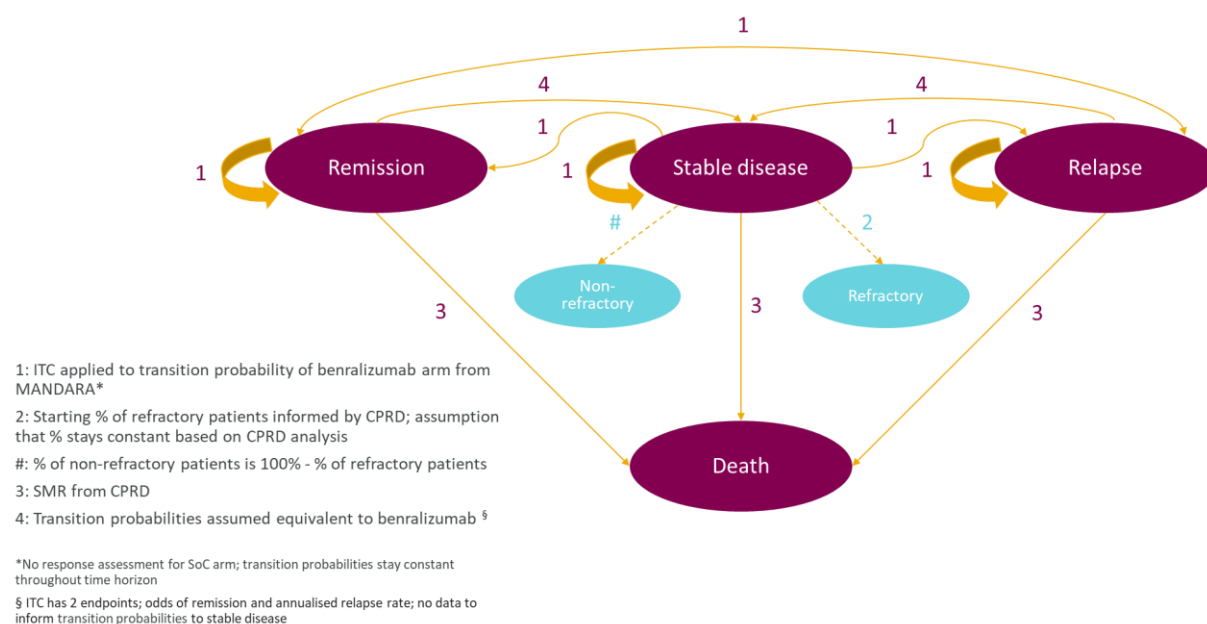
B1. Model transitions to the relapse state

Priority question: Figure 12, page 77 of the CS Doc B,⁵ indicates that in the economic model for benralizumab it is possible for patients to transition to the relapse state from the remission state or the stable state. Figure 13, page 78 of the CS Doc B,⁵ indicates that in the economic model for SoC there are 2 arrows going from relapse to stable and no arrows going the other way.

- a) For SoC, please confirm if there is an error in the diagram regarding the arrow directions, and which evidence source informs transitions from stable to relapse and from relapse to stable.

Yes, there is an error in the diagram. An updated version has been provided in Figure 7.

Figure 7: Model structure parameterisation by treatment arm – SoC arm (update of Figure 13 from company submission Document B)



Abbreviations: CPRD: Clinical Practice Research Datalink; ITC: indirect treatment comparison; SMR: standardised mortality ratio; SoC: standard of care

A comprehensive overview of the approach adopted to inform transition probabilities in the economic model, by treatment arm, is provided in Appendix 1. This question focuses on specific transitions in the SoC arm – so the relevant information is provided below.

The transition from stable disease to relapse in the SoC arm was informed by a stepwise approach, outlined below:

- The transition probability from stable disease to relapse was first derived for the benralizumab arm from MANDARA.
- As outlined in response to question B.4 (a), with no evidence to inform transition probabilities for SoC, the benralizumab arm informed the baseline risk transition probabilities and the outcomes of the ITC were applied to the benralizumab arm to generate the transition probabilities for the SoC arm.
- To inform the specific transition from stable disease to relapse in the SoC arm, the rate ratio (RR) of the annualised relapse rate from the ITC was applied to the transition probability from the benralizumab arm.

The ITC informed transitions to remission (odds of remission endpoint) and transitions to relapse (annualised relapse rate endpoint) – however, no data were available to inform transitions to stable disease. In light of this, the transition from relapse to stable disease was assumed equivalent to that in the benralizumab arm.

b) Please clarify the possible changes in the disease that may explain a transition from the stable state to the relapse state.

Patients residing in the stable disease health state will transition to the relapse state due to any of the reasons listed as part of the definition of relapse (see Figure 1):

- An increase in BVAS to a score >0 due to active vasculitis
- Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score
- Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions;

warranting any of the following:

- An increased dose of OCS therapy to >4 mg/day; OR
- An increased dose or addition of IS therapy; OR
- Hospitalisation related to EGPA worsening.

c) In the annualised relapse rate ITC analysis, did the number of relapses include both cases of patients previously in the stable state and in the remission state?

Yes, the number of relapses included both patients previously in the stable state as well as patients in the remission state.

d) What percentage of patients in the Mandara trial who were classified as having relapsed were previously in remission, and what percentage were previously in the stable state?

Table 20 presents the proportion of patients in the MANDARA trial who were classified as having relapsed and were previously in remission or stable disease states. These transition counts informed the transition matrices.

Table 20: MANDARA trial participants who transitioned from remission or stable disease to relapse

Starting disease state	End disease state		
	Relapse		
	Transition counts	N (patients in relapse)	%
All benralizumab patients^a			
Remission	■	■	■
Stable disease	■	■	■
Benralizumab responders^b			
Remission	■	■	■
Stable disease	■	■	■

Footnotes: ^a All benralizumab patients refer to the whole cohort of 70 patients enrolled in the MANDARA trial, in the benralizumab arm, analysed over 52 weeks of follow-up.

^b Benralizumab responders refer to the subgroup of 46 patients who responded (response defined as BVAS=0 and an OCS dose ≤4 mg/day) to benralizumab, analysed over 52 weeks of follow-up.

Source: Analysis was based on IPD from MANDARA

- e) **What percentage of patients in the Mirra trial who were classified as having relapsed were previously in remission, and what percentage were previously in the stable state?**

Responding to this question would require access to MIRRA IPD which AstraZeneca does not have – and therefore, is unable to provide a response.

B2. Adelphi DSP study

- a) Please provide the patient characteristics by disease state for which utilities were estimated.

Patient characteristics are available for the whole cohort (177 patients who completed the EQ-5D questionnaire and had an EQ-5D score available) – not by disease state. Table 21 presents the patient characteristics for these 177 patients.

Table 21: Adelphi DSP patient characteristics

Characteristics	n	%
Patient age		
Mean, years	■	■

<18years	■	■
≥18years	■	■
Patient sex		
Male	■	■
Female	■	■
Country of residence		
France	■	■
Germany	■	■
Italy	■	■
Spain	■	■
UK	■	■
US	■	■
Ethnicity^a		
White	■	■
Black (African American, African or Caribbean)	■	■
BMI		
Underweight	■	■
Healthy weight	■	■
Overweight	■	■
Obese	■	■

Footnotes: ^a Only available for ■ participants

Abbreviations: BMI: body mass index; DSP: disease specific programme.

Source: AstraZeneca. Data on File. Adelphi DSP Study Results³⁴

- b) Please clarify whether the utility values are unadjusted or adjusted for patient characteristics.

Utility values were not adjusted for patient characteristics. The study was not powered to detect differences in HRQoL between patient groups; therefore, adjustment would not be appropriate.

Note – age-adjusted utility values were implemented in the model to account for the expected decrease in HRQoL over time associated with aging.

- c) Please explain how the non-refractory utility estimate used in the model was derived.

The non-refractory utility was derived from an average of the following disease states: “remain stable” and “improve slowly” – these are representative of patients with non-refractory disease, as validated by clinical experts.⁹ The average utility was [REDACTED] for patients in the “non-refractory” disease state.

Table 22 presents further detail on the approach undertaken to derive the non-refractory utility estimate.

Table 22: Non-refractory disease state utility

Disease state	Disease state utility			
	N	Mean	SD	SE
Remain stable*	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Improve slowly*	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non-refractory (Derived)		[REDACTED]	[REDACTED]	[REDACTED]

Footnotes: *Measured empirically in the Adelphi DSP study

^a non-refractory SD estimated using the formula outlined below

$$\sqrt{\frac{SD_{remain\ stable}^2 + SD_{improve\ slowly}^2}{n}}$$

^b non-refractory SE estimated using the formula $SD/\sqrt{n}$

Abbreviations: N: Sample size; SD: Standard deviation; SE: Standard error

d) Please provide the confidence intervals for the utility estimates.

Table 23 presents the confidence intervals (CIs) for the utility estimates.

Table 23: Adelphi DSP utility estimate confidence intervals

Disease state	Utility estimate	Lower CI	Upper CI
Remission	[REDACTED]	[REDACTED]	[REDACTED]
Non-refractory	[REDACTED]	[REDACTED]	[REDACTED]
Refractory	[REDACTED]	[REDACTED]	[REDACTED]
Relapse	[REDACTED]	[REDACTED]	[REDACTED]

Footnotes: ^a 95% CI for non-refractory disease state estimated using derived standard error

Abbreviations: CI: confidence interval

B3. UK-specific Vignette studies

a) Please provide the number of patients and the patient characteristics by disease state for which utilities were estimated.

Patient characteristics are available for the whole cohort (patients who completed the EQ-5D questionnaire and had an EQ-5D score available [Table 24]) – not by disease state.

Table 24: UK-specific vignette study patient characteristics (N=20)^a

Characteristic		Value
Age (years)	Mean (SD)	██████
	Range	████
Sex	Female	██████
	Male	██████
Ethnicity	White	██████
Employment	Employed full-time	██████
	Employed part-time	██████
	Retired	██████
	Unable to work due to your health	██████
	Unemployed/looking for work	██████
Time since EGPA diagnosis (years) ^b	Mean (SD)	██████
	Range	██████
Previously hospitalised due to EGPA	Yes	██████
	No	██████
Current treatment(s)	Biologics	██████
	IS and Biologics	██████
	OCS, IS, and Biologics	██████
	IS	██████
	OCS	██████
	OCS and IS	██████
	None of the above	██████

Footnotes: ^a Data were collected from N=21 patients, but one patient was excluded from the analysis due to the researcher deeming they were not paying attention to the task

^b n=1 patient did not answer this question because they could not remember

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis; IS: immunosuppressant; OCS: oral corticosteroids; SD: standard deviation; VAS: visual analogue scale

Source: AstraZeneca. Data on File. Vignette results. 2025³⁵

b) Did every participant provide a utility estimate for each health state?

Yes, every participant provided a utility estimate for each health state.

c) Please provide the confidence intervals for the utility estimates.

Table 25 presents the CIs for the utility estimates, derived from the general public and patient valuation.

Table 25: UK-specific vignette study utility estimates

Disease state	General public (N=316)		Patients with EGPA (N=20) ^a	
	Mean utility estimate	95% CI	Mean utility estimate	95% CI
Remission	████	██████	████	██████
Non-refractory	████	██████	████	██████
Refractory	████	██████	████	██████
Relapse	████	██████	████	██████

Footnotes: ^a Data were collected from N=21 patients, but n=1 patient was excluded from the analysis due to the researcher deeming they were not paying attention to the task

Abbreviations: CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis

Source: AstraZeneca. Data on File. Vignette results. 2025³⁵

B4. Constant baseline risk probabilities during lifetime?

Priority question: The SoC remission/stable/relapse transition probabilities were derived from the benralizumab transition probabilities and, in most cases, using the Bucher ITC estimates. Since the benralizumab transition probabilities are assumed to be constant over time after 52 weeks, the implication is that the SoC transition probabilities are constant over time as well. Clarification A10 concerns the issue of no waning of effectiveness of benralizumab. This question concerns the baseline risk transition probabilities. The baseline risk transition probabilities in this submission are those of benralizumab.

- a) Are the baseline risk transition probabilities in this submission those of benralizumab because there is no evidence to inform transition probabilities for SoC?**

Yes, with no evidence to inform transition probabilities for SoC, the benralizumab arm informed the baseline risk transition probabilities and the outcomes of the ITC were applied to the benralizumab arm to generate the transition probabilities for the SoC arm. Further context is provided below.

The MANDARA trial provided a comparison of the efficacy of benralizumab vs mepolizumab, however, mepolizumab is not a relevant comparator for this evaluation as it is not a reimbursed treatment option in the UK. As per the decision problem, the relevant comparator is SoC in UK clinical practice, consisting of OCS with or without IS. Given the lack of head-to-head trial informing the relative efficacy of benralizumab vs SoC in patients with EGPA, an ITC was conducted to generate comparative efficacy estimates.

SoC in MIRRA, consisted of OCS with or without IS, which was reflective of UK clinical practice. Therefore, use of data from the SoC arm of MIRRA produced an indirect comparison of benralizumab vs SoC that was generalisable to UK clinical practice.

A comprehensive overview of the approach adopted to inform transition probabilities in the economic model, by treatment arm, is provided in Appendix 1.

b) On page 87 of the CS Doc B it refers to the percentage of patients in refractory being constant over 5 years.⁵ Was this the sole justification for constant SoC transition probabilities over time, or were there other justifications?

The CPRD study provided evidence that the proportion of patients with refractory disease did not change over 5 years. Therefore, the assumption of the proportion of patients with refractory disease being constant over 5 years is based on these empirical data, representative of UK patients. This assumption was validated during interviews with clinical experts.⁹

Importantly, the proportion of refractory patients being constant over time is not linked to transition probabilities for SoC. A comprehensive overview of the approach adopted to inform transition probabilities in the economic model, by treatment arm, is provided in Appendix 1.

c) In the CS Doc B page 124, the external validity section seems to discuss internal validity. Please present comparisons of model predictions at appropriate points over time of survival, OCS chronic and acute conditions and the percentages in each EGPA state (of starting cohort or of patients still alive) with published evidence or evidence from company analysis (such as of the CPRD data) for SoC. If there is no external patient data against which to conduct external validation of model predictions, did the company's clinical experts provide an opinion on the validity of these predictions?

AstraZeneca thank the EAG for bringing this to our attention.

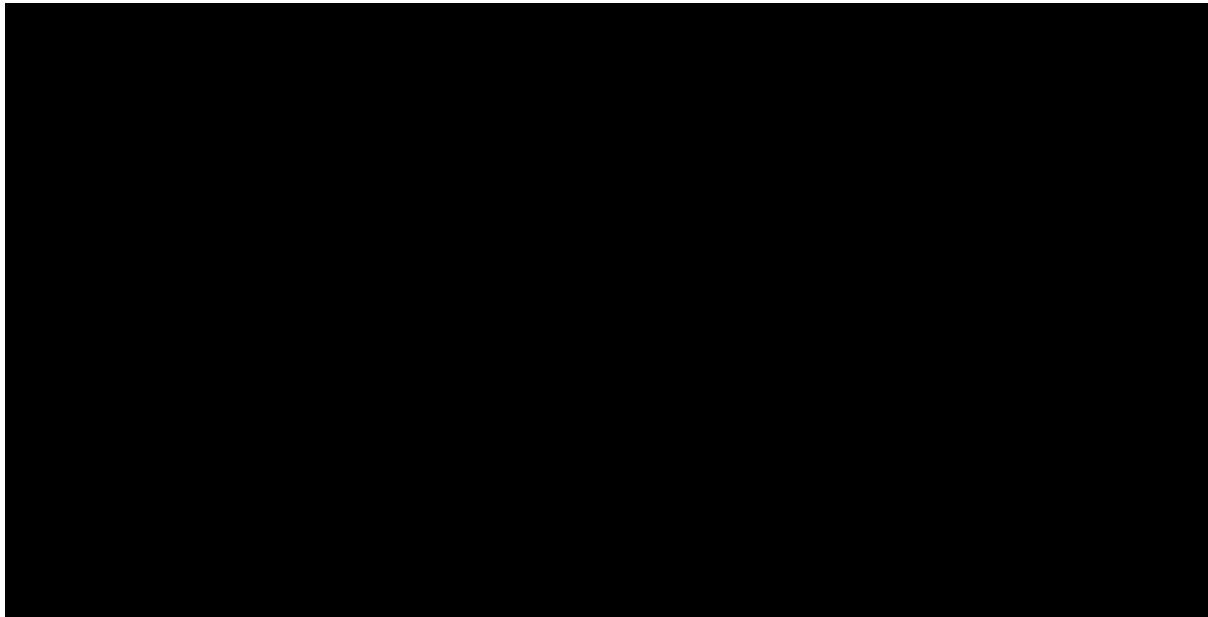
Figure 8 to Figure 14 present model predictions, by treatment arm, over the time horizon for the below outcomes:

- Survival
- OCS-related chronic events
- OCS-related acute events
- Proportion of patients in each EGPA state

There is no external patient data against which to conduct external validation of long-term model predictions. Additionally feedback was elicited from two of the three clinical experts who

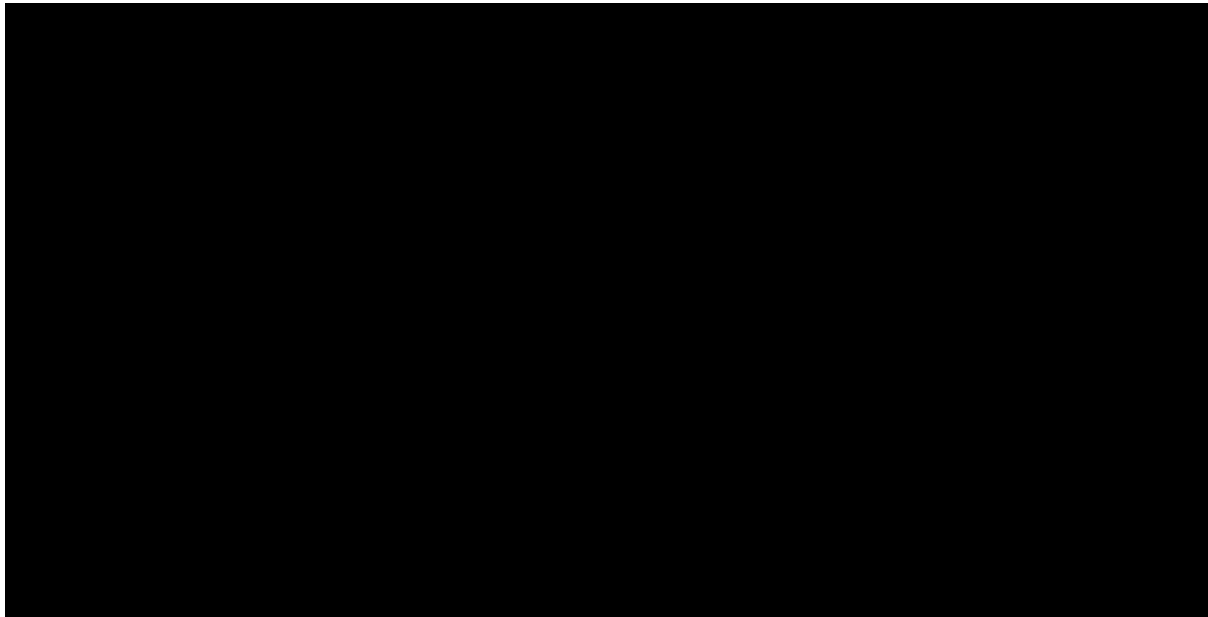
participated in the original clinical expert interviews (Data on File 3⁹). Clinical experts thought that in general, the model outputs were in line with expectations for a non-severe EGPA population.¹⁶

Figure 8: Model prediction of survival by treatment arm



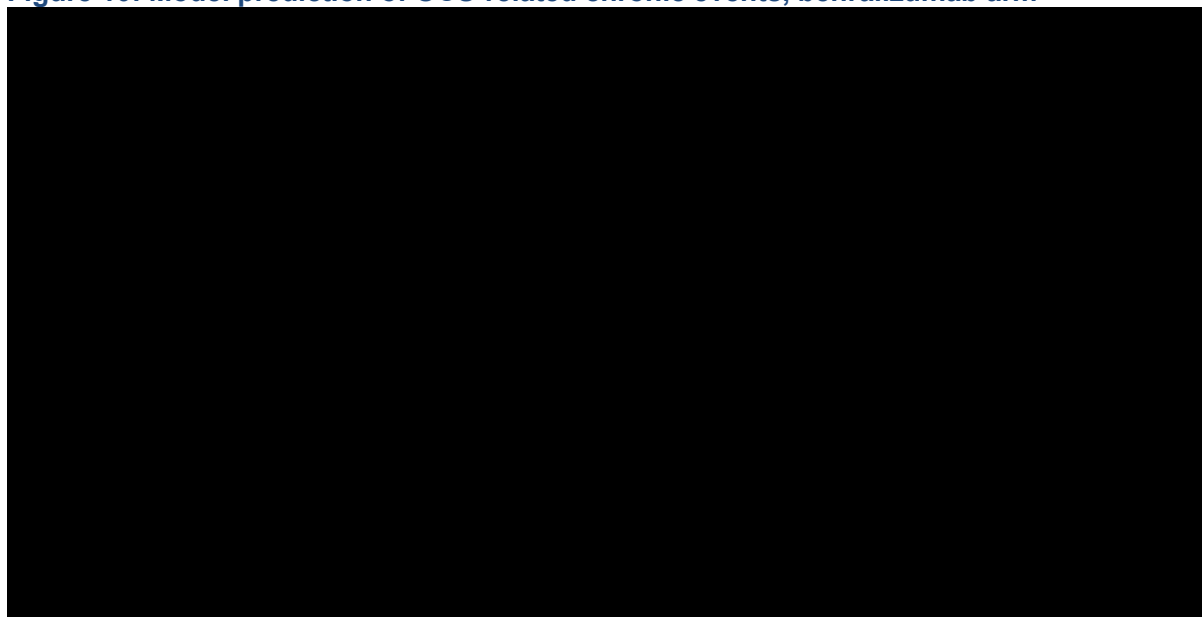
Abbreviations: SoC: standard of care

Figure 9: Model prediction of OCS-related chronic events, SoC arm



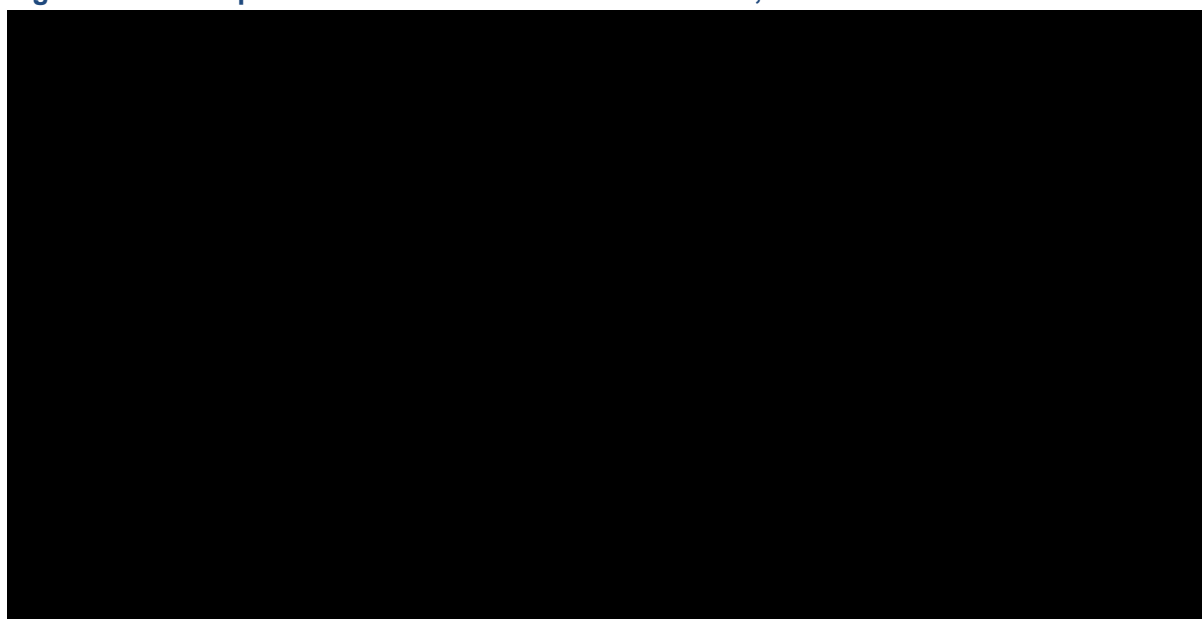
Abbreviations: eCVD: established cardiovascular disease; OCS: oral corticosteroids; SoC: standard of care; T2DM: Type-2 diabetes mellitus

Figure 10: Model prediction of OCS-related chronic events, benralizumab arm



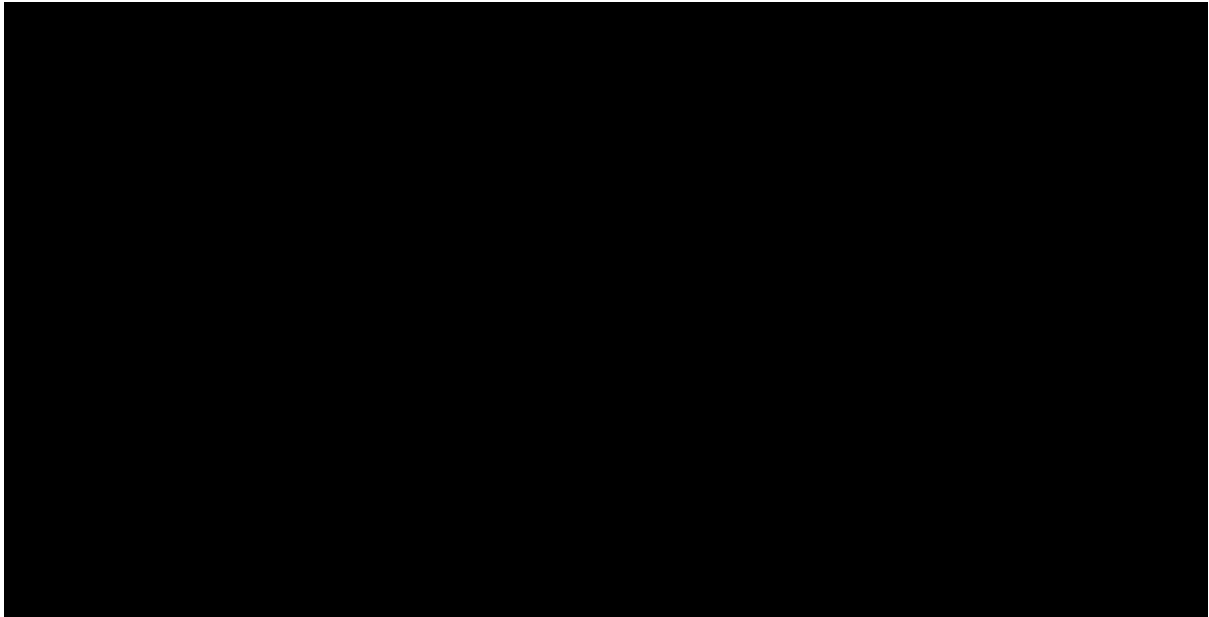
Abbreviations: eCVD: established cardiovascular disease; OCS: oral corticosteroids; T2DM: Type-2 diabetes mellitus

Figure 11: Model prediction of OCS-related acute events, SoC arm



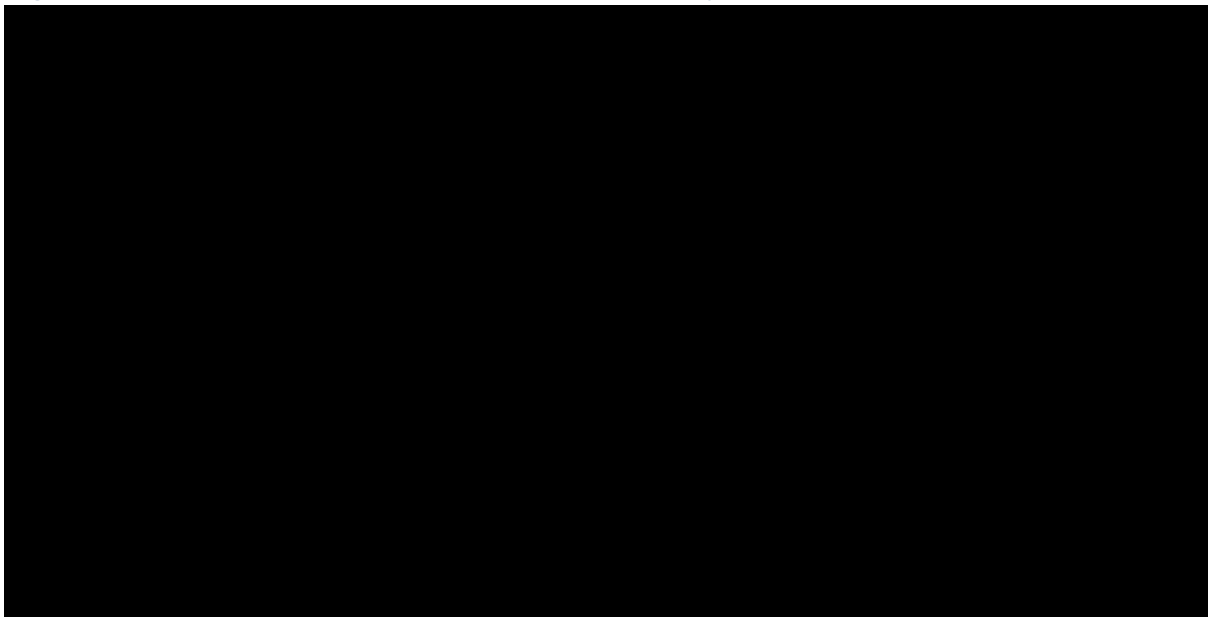
Abbreviations: OCS: oral corticosteroids; SoC: standard of care

Figure 12: Model prediction of OCS-related acute events, benralizumab arm



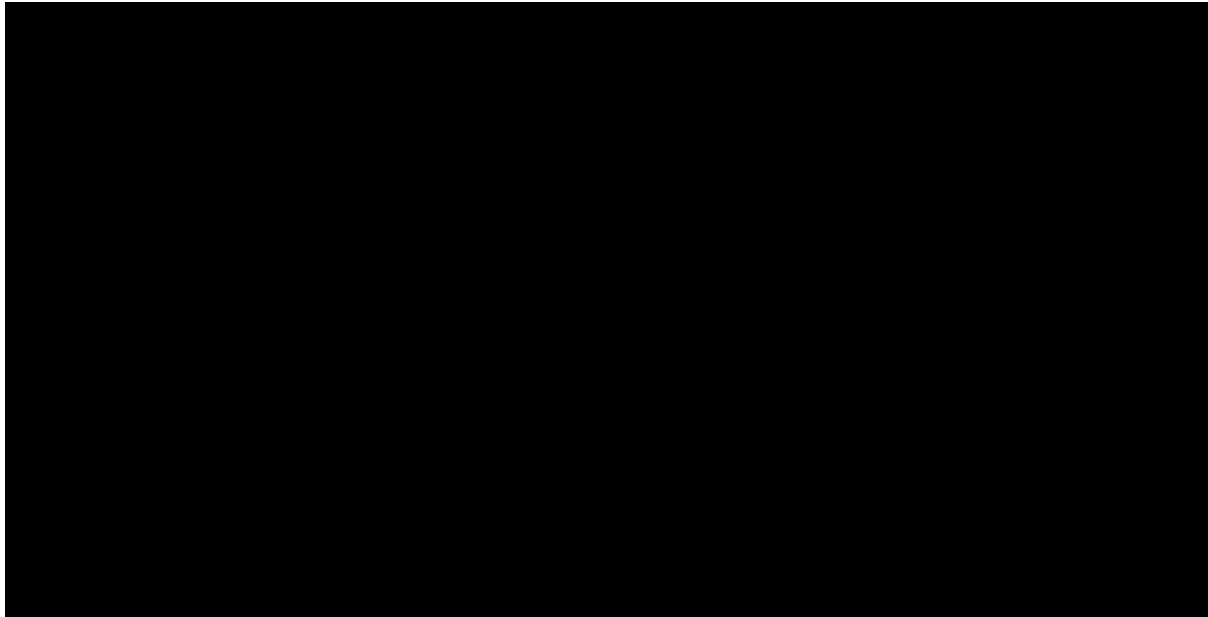
Abbreviations: OCS: oral corticosteroids

Figure 13: Model prediction of health state occupancy; SoC arm



Abbreviations: SoC: standard of care

Figure 14: Model prediction of health state occupancy; benralizumab arm

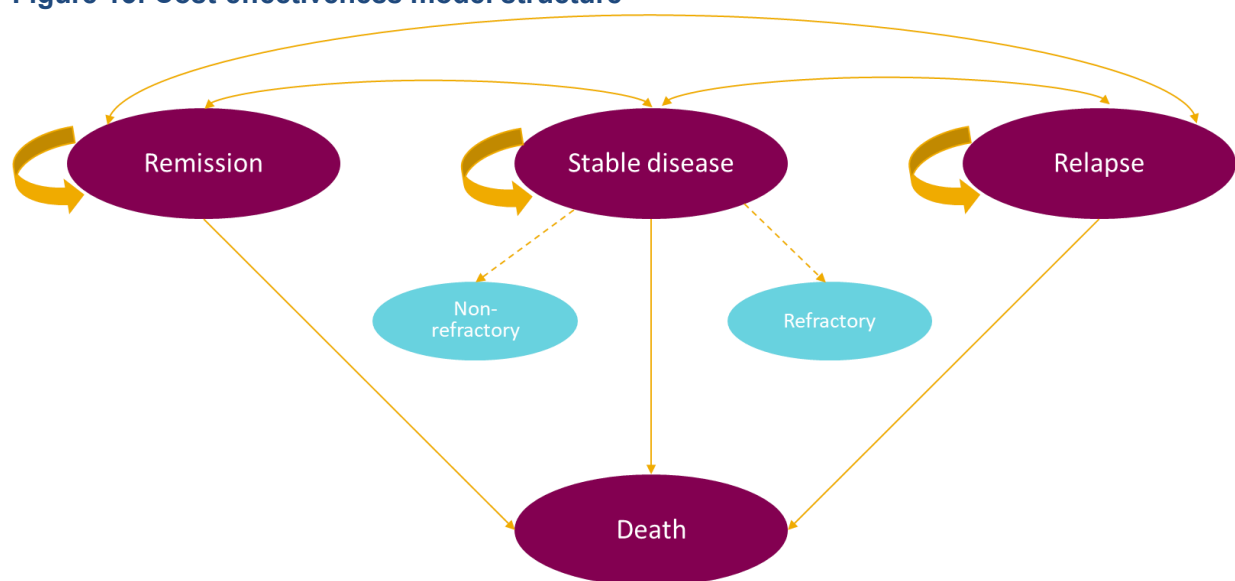


B5. First year transition probabilities

- a) Please provide the dataset used to estimate the benralizumab transition probabilities.

The cost-effectiveness model featured three mutually exclusive, alive health states – which comprehensively captured the disease evolution; namely remission, stable disease, relapse – as well as a death state (Figure 15). Due to the limited sample size in MANDARA (N=70 patients in the benralizumab arm), transition probabilities to and from the non-refractory and refractory health states from other health states could not be derived from the trial data. Given these data limitations, the refractory and non-refractory health states were modelled as sub-states within the stable disease health state.

Figure 15: Cost-effectiveness model structure



Footnotes: Purple boxes denote health states; blue boxes denote sub-states where patients were subject to sub-state specific utilities

Abbreviations: EGPA: eosinophilic granulomatosis with polyangiitis

The dataset used to estimate the benralizumab transition probabilities is provided (Table 26), in the form of transition counts stratified by all benralizumab patients and benralizumab responders from MANDARA.

Table 26: Dataset from MANDARA used to estimate benralizumab transition probabilities

Starting disease state	End disease state		
	Remission	Stable disease	Relapse
All benralizumab patients^a			
Remission	■	■	■
Stable disease	■	■	■
Relapse	■	■	■
Benralizumab responders^b			
Remission	■	■	■
Stable disease	■	■	■
Relapse	■	■	■

Footnotes: ^a All benralizumab patients refer to the whole cohort of 70 patients enrolled in the MANDARA trial, in the benralizumab arm, analysed over 52 weeks of follow-up.

^b Benralizumab responders refer to the subgroup of 46 patients who responded (response defined as BVAS=0 and an OCS dose ≤4 mg/day) to benralizumab, analysed over 52 weeks of follow-up.

Source: Analysis was based on IPD from MANDARA

b) Please provide the model syntax used to estimate the transition probabilities if a model such as that specified in Welton et al. (2012) was used.³⁶

The syntax used to generate the transition probabilities is provided below. The model was run with 3 chains with 20,000 simulations each.

```
model{
  for (i in 1:3){
    r[i,1:3] ~ dmulti(pi[i,1:3],n[i])
    pi[i,1:3] ~ ddirch(prior[i,1:3])
  }
  for (i in 1:3){
    for (j in 1:3){
      rhat[i,j]<-pi[i,j]*n[i]
    }
  }
}
```

```

dev[i,j]<-2*r[i,j]*log(r[i,j]/rhat[i,j])

}

resdev[i]<-sum(dev[i,1:3])

}

resdevtot<-sum(resdev[1:3])

}

```

B8. CPRD analysis

- a) Please provide a summary of the statistical methods used to evaluate whether or not the percentages of treatment use and whether the percentage refractory varied over time.

No formal longitudinal analysis was conducted as part of the CPRD study. The results were descriptive analyses, with the distribution of health states described at index, and then at regular intervals during follow-up (e.g. every 6 months for 2 years, annually for years 3–5).

Based on Occam's razor, in the absence of evidence that the proportion of patients with refractory disease varies over time, it is appropriate to conclude that it does not.

- b) Please explain how the 486 people with EGPA included in the CPRD analysis were identified in order to ensure it was representative of the population in England.

The 486 patients included were all identified incident cases in the study period 1/1/2006 to 28/2/2019 from CPRD Aurum, which is representative of the English population.^{9, 37} Given the study included all available incident cases within a representative database, it can be concluded that the sample of patients with EGPA is representative of the population of patients with EGPA in England.

The full inclusion criteria are provided below:

All EGPA patients

Inclusion criteria

- At least one EGPA diagnosis code identified through GP visits (CPRD Aurum) or inpatient admissions (HES APC) during 1 January 2006 to 28 February 2019. Patients with an EGPA diagnosis record before this period are included as long as they have at least one EGPA diagnosis record during 1 January 2006 to 28 February 2019.
- An acceptable patient's data-quality flag.
- Eligible for linkage to the Hospital Episode Statistics inpatient, outpatient and accidents and emergencies records and the ONS death data from the UK.

- Contributing at least one day in the CPRD database after index date.

Exclusion criteria

Patients with any of the following diagnosis first occurring after most recent EGPA diagnosis record will be excluded:

- Wegener's granulomatosis or granulomatosis with polyangiitis (GPA); or
- Microscopic polyangiitis (MPA); or
- Polyarteritis nodosa; or
- Takayasu arteritis; or
- Giant cell arteritis.

Incident EGPA patients

The incident EGPA cohort is a subset of the All EGPA patient population with the following additional exclusion criteria applied:

- At least 12 months look-back period before and inclusive of the index date.
- Patients with an EGPA diagnosis record prior to 1 January 2006 in CPRD Aurum or HES APC databases are excluded from the incident cohort. To avoid overestimation of incident diagnoses, individuals must have at least 12 months of available data prior to the index date to be included in the calculation of incidence rates.

Details of the EGPA code are provided as Data on File.³⁸

- c) Please describe how the mg/day dose estimates for the SoC treatments were calculated.

The approach adopted is described below:

Drug therapy variables were created from records with valid information. Medication was only recorded in primary care (CPRD Aurum), not in the hospital database (HES), so all drug information was captured solely from CPRD Aurum, specifically in the table Drug Issues. Medications were identified using code lists from the relevant CPRD Aurum prodcode mapped to the Dictionary of Medicines and Devices (dm+d) codes. Prescription records in CPRD Aurum which have a quantity of zero or negative and duration of zero recorded were excluded from any analysis. Missing or invalid values in other variables describing the prescription such as dosage, quantity unit identifier, or cost, were allowed.

A prescription of EGPA medication was defined using relevant product codes in the patient therapy record. The following definitions were applied:

- Treatment discontinuation: the most prescribed duration of each substance in the incident cohort was 28 days. Treatment discontinuation was defined as 60 days with no prescriptions of each substance.
- Prescription estimated duration: First, the time between one prescription and the next was calculated. For time between prescriptions below the treatment discontinuation gap for each substance the time between prescriptions was assumed to be the real duration. For those

prescriptions with a time gap between prescriptions greater than the treatment discontinuation gap:

- if the duration was available, it was used for the determination.
 - if the duration of the prescription was missing or equal to zero, the median duration, for similar prescriptions with the same strength and quantity, was estimated and imputed.
 - in case of insufficient data to estimate the median (all duration equals to zero or only one prescription for a specific strength and quantity) a fixed value of 28 days was imputed (most frequently duration prescribed).
- Dosage: The daily dose was calculated as the product of quantity and substance strength, divided by the prescription estimated duration. In case of two prescriptions in the same day, the substance strength was added, and average quantity and prescription estimated duration was used for the calculation.
 - Medication exposure episode: exposure episode was defined as the time from index date to treatment discontinuation date.

d) Please explain what, if any, steps were taken in the CPRD resource use analysis for remission/stable/relapse states to avoid capturing resource use associated with OCS adverse events which have been costed separately.

The health-state specific resource use, informed by the CPRD analysis, were “all-cause resource use related to an EGPA diagnosis”. This was deemed the most appropriate and robust data source to inform HCRU in the company submission (CS), because the reported frequency was too low for robust analyses, and resource use for outpatient visits, emergency department (ED) visits and critical care visits were unavailable in the alternative data input “EGPA-related HCRU” (as shown in Table 27). Nonetheless, a sensitivity analysis was run using the EGPA-related HCRU, with a minimal impact on the cost-effectiveness results; the deterministic ICER increased to £28,146 (previously £25,314).

Table 27: All cause and EGPA-related healthcare resource use from CPRD

Resource	Remission	Stable disease	Relapse
All-cause HCRU			
GP consultations	■	■	■
Nurse consultations	■	■	■
Outpatient visits	■	■	■
ED visits	■	■	■
Hospitalisations	■	■	■
Critical care visits	■	■	■
EGPA-related HCRU			
GP consultations	■	■	■
Nurse consultations	■	■	■

Outpatient visits	■	■	■
ED visits	■	■	■
Hospitalisations	■	■	■
Critical care visits	■	■	■

Abbreviations: ED: emergency department; EGPA; eosinophilic granulomatosis with polyangiitis; GP general practitioner; HCRU: healthcare resource use

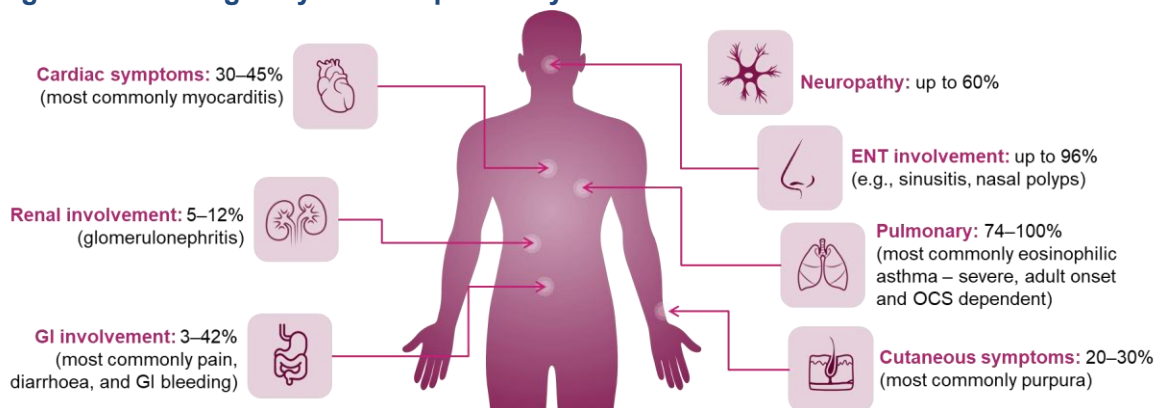
Source: CPRD Analysis

B9. EGPA manifestations

- a) Please list the 2-4 EGPA manifestations other than asthma/respiratory/ENT that are the most severe for patients.

Considering the multi-system impact of EGPA, patients experience a broad range of immediate manifestations; commonly reported symptoms are outlined in Figure 16 below.

Figure 16: The organ systems impacted by EGPA



Abbreviations: ENT: ear-nose-throat; GI: gastrointestinal; OCS: oral corticosteroid

Source: Adapted from Trivoli G, *et al.* Rheumatology 2020;³⁹ Cottin V, *et al.* European Respiratory Journal;⁴⁰ Doubelt I, *et al.* ACR Open Rheumatology⁴¹

“Severe” manifestations can be interpreted as either impacting the daily life of EGPA patients e.g. neuropathy manifestations leading to mobility challenges or increasing their mortality long-term e.g. cardiac manifestations. Some manifestations other than asthma/respiratory and ENT are listed below:

- Cardiac (cardiac myopathy, pericarditis, myocarditis)⁷
- Renal (active glomerulonephritis, hypertension, proteinuria, haematuria, progressive glomerulonephritis, and kidney failure)⁴²
- Gastro-intestinal (GI) involvement (severe GI tract involvement, GI bleeding, abdominal pain and colitis)³⁹
- Neuropathy^{43, 44}

- b) Are the manifestations in (a) related to established stages of disease for EGPA?

EGPA is described as having three phases: the prodromal (allergic), eosinophilic, and vasculitic phases.⁴⁵

- The prodromal phase is characterised by adult-onset eosinophilic asthma.
- In the eosinophilic phase, clinical symptoms are due to eosinophilic organ infiltrates that typically affect the lungs, GI tract, and heart.
- The vasculitic phase is mediated by eosinophilic infiltration, eosinophilic vasculitis, and extravascular eosinophilic granulomas, which can cause damage to the nervous system, skin, and kidneys, although every organ may be affected.

Recent understanding is that these phases may overlap, may not appear sequentially, or may not occur in every patient.³⁹ Even within each phase, clinical presentation and quality of life will vary substantially dependent upon the level of disease control. The most severe manifestations of EGPA, listed in the response to question B.9 (a), are related to the second “eosinophilic” phase and final “vasculitic” phase of EGPA. Cardiac and GI manifestations occur in the eosinophilic phase. Renal manifestations and neuropathy commonly occur in the vasculitic phase.

c) Do the manifestations in (a) have an effect on the HRQoL of patients independently of the chronic and acute adverse events associated with OCS treatment?

Yes, all the manifestations impact a patient’s quality of life independently from the QoL shortcomings associated with OCS treatment.

OCS treatments are associated with acute and chronic AEs, including type 2 diabetes mellitus (T2DM), cardiovascular disease, osteoporosis, pneumonia, cataracts, and sleep apnoea, amongst other conditions. These adverse events differ from the symptoms associated with EGPA manifestations which impact a patient’s HRQoL.

As discussed in the submission section B.1.3.2, the manifestations of EGPA create long term health consequences that reduce a patients HRQoL.⁴⁶ The response to question B.9 (d) details the HRQoL impact of the manifestations stated in B.9 (a). The HRQoL impact of the manifestations of EGPA were captured in the cost effectiveness model within the health state utilities, separate to the HRQoL impacts of OCS-related AEs.

d) Please provide HRQoL evidence for the manifestations.

Patients with cardiac manifestations can experience symptoms including shortness of breath, chest pain and irregular heartbeat, with further disease progression resulting in heart failure, heart attack and thrombosis. This can lead to impairment in social functioning, mental health, perceptions of general health, sleep, and vitality as well as leading to anxiety and depression.⁴⁷ Further HRQoL issues as a result of cardiac manifestations are inability to exercise, fear of recurrent issues, interruption of daily activities, absenteeism and impaired ability to do housework.⁴⁸

Patients with renal manifestations can experience symptoms like fatigue, tiredness, loss of appetite and nausea. This can impact the ability of people with EGPA to socialise, with the fatigue preventing patients holding down a steady job.⁴⁹ Patients with kidney failure, a severe

renal manifestation, may require dialysis which can be time consuming and inconvenient because they are required to regularly travel to a hospital to receive the treatment.^{50, 51}

Patients with GI manifestations experience nausea, vomiting and diarrhoea which can lead to psychosocial impacts such as impaired quality of life, comorbid psychiatric disorders, chronic life stress and impaired coping. GI manifestations affect daily performance and productivity in a patient's working life and can lead to a greater extent of short periods of sick leave.⁵²

Patients with neuropathy may have weakness in limbs, loss of feeling, tingling or paralysis in areas of the body. This can result in difficulties with walking, standing, lifting and carrying objects, impacting an individual's ability to carry out daily activities and work.^{53, 54}

- e) Please provide evidence on the time to development of the manifestations listed in (a) from EGPA diagnosis.

There is limited literature to inform this response; therefore, clinical experts have been consulted.¹⁶ The development of manifestations is not time dependent. A patient could have been diagnosed with EGPA very recently and present with cardiac, renal, or GI manifestations. Conversely, a patient could have had EGPA for a significant period but never experienced these manifestations.

B10. IS treatment adverse events

- a) What, if any, severe adverse events are associated with IS treatment?

IS treatment is associated with a high risk of organ toxicity and side effects including, but not limited to, cytopenia, hepatotoxicity, and major infections such as bacterial pneumonias herpes zoster recurrences, opportunistic infections and Pneumocystis jiroveci pneumonia.⁵⁵⁻⁵⁸

- b) Is there overlap in the SAEs associated with IS treatment and OCS treatment?

OCS and IS have different mechanisms of action, so there is no overlap in the serious adverse events associated with OCS and IS treatment.

- OCS are anti-inflammatory treatments and directly target EOS. They are associated with acute and chronic AEs, including T2DM, cardiovascular disease, osteoporosis, pneumonia, cataracts and sleep apnoea.⁴⁶
- IS suppress the immune system without specifically targeting hypereosinophilia in EGPA.⁵⁵⁻⁵⁸

Adverse events associated with OCS are broader and do not occur as a consequence of immune system suppression, whereas adverse events associated with IS treatment are caused by immune system suppression only. AEs caused by IS use are outlined in response B.10 (a).

- c) How significant is the impact on HRQoL of the IS treatment adverse events?

IS contribute to the HRQoL burden experienced by patients with EGPA. The side effects of IS have a negative impact on quality of life, adding to the physical and mental burden for patients and requiring more frequent healthcare visits. Patients who develop cytopenia following IS

treatment may experience symptoms of fatigue, weakness, dizziness and poor concentration.⁵⁹ This can reduce their HRQoL and impair their ability to work.

- d) Please provide any evidence on the time to development of SAEs associated with IS treatment.

There is limited literature to inform this response; therefore, clinical experts have been consulted.¹⁶ AEs such as infections and hepatotoxicity generally appear quickly after IS treatment (e.g. 3 months) whereas cytopenia is a late complication which can appear after long-term IS treatment (e.g. 3 years).

B11. Modelling responders for benralizumab after 1 year

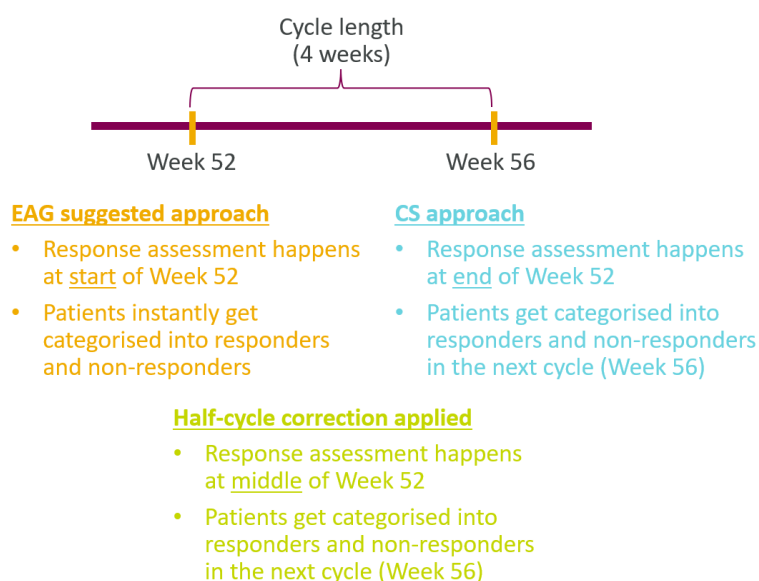
- a) In the economic model, it appears that patients who initially respond at 52 weeks, defined by the remission state at 52 weeks, who subsequently transition to a stable or relapse state continue to receive benralizumab. Please explain the rationale for this assumption.

AstraZeneca thank the EAG for bringing this to our attention. The model has now been updated, such that all patients who respond at 52 weeks (defined as BVAS=0 and OCS dose $\leq 4\text{mg/day}$) continue to receive benralizumab, and all patients in the stable or relapse states discontinue benralizumab and receive standard of care (SoC). This revision had a minimal impact on the results; the deterministic ICER increased to £26,092 (previously £25,314). A revised version of this model has also been submitted alongside responses.

- b) In the economic model, no matter the state of patients at 52 weeks, roughly ■% of patients receiving benralizumab are assumed to be responders and therefore in week 56 the percentages of patients in each of the remission/stable/relapse states are calculated as the sum product of the transition probabilities and the state percentages multiplied by ■%. Please comment on why the predicted percentage of patients in the model at 52 weeks did not match the ■%.

It was assumed that the clinical response assessment would take place at the end of Week 52; therefore, patients would move to the responder health state at the next modelled cycle, i.e. Week 56. This is why approximately ■% of patients receiving benralizumab appear to be responders at Week 56 instead in the company submission model. In real life, time is continuous, and patients would therefore discontinue the next day post-assessment; however, for the purpose of the economic model, the cycle length is a discrete period of time (4 weeks). Therefore, patients discontinue at the start of Week 56. Of note, this approach has limited impact on the results as the half-cycle correction would further adjust for this – see Figure 17.

Figure 17: Benralizumab response assessment overview



Abbreviations: CS: company submission

B12. Refractory percentages

Every patient has stable disease at baseline, therefore the █ of patients in the benralizumab who were refractory represents the percentage of stable patients.

a) Page 88, CS Doc B. Please clarify if the █% of benralizumab patients at 52 weeks is the percentage of stable patients at 52 weeks.⁵

- As discussed during the clarification call, the initial statement is incorrectly framed; the █% represents the proportion of the total MANDARA population who had refractory disease at baseline – not the proportion of patients with stable disease. Stable disease is an umbrella term for patients with refractory and non-refractory disease.
- In MANDARA, there were █% of patients with refractory disease (not stable disease) in the benralizumab arm at 52 weeks.

b) Please confirm that you have assumed a linear reduction in the percentage of stable patients who are refractory from █% to █%.

Yes, a linear reduction was applied from baseline to Week 52 in the economic model over each cycle (every 4 weeks). Therefore, an absolute reduction of █% was applied every cycle (every 4 weeks) to the proportion of patients with refractory disease.

B13. Risk of OCS-related adverse events

The risk of OCS-related adverse events is modelled as a non-linear relationship to the cumulative OCS dose. The method used assumes that the OCS dose is

cumulative. Please explain the clinical basis for the risk of adverse events being related to cumulative OCS dose over all years, rather than, say, the last few years; e.g. why is it not possible that if someone is in remission for a few years, their risk of OCS adverse events does not fall?

Evidence from literature suggests that the risk of OCS-related AEs is correlated with cumulative OCS exposure over all years.

Further detail is provided below:

- Data linking the incidence of AEs and cumulative OCS exposure are well cited within the literature with recent evidence demonstrating that as little as 0.5–1.0 g (equivalent to 2–4 lifetime courses) of cumulative exposure to OCS is associated with adverse outcomes.^{46, 60}
- Each year of exposure to any OCS prescription results in a higher subsequent likelihood of AEs. Each prior year (at any point before the current year) of exposure to 1 to 3 prescriptions resulted in 1.07 times the odds of having a new AE in the current year whilst exposure to ≥ 4 prescriptions in any prior year resulted in an odds ratio of 1.20.⁶¹
- Even intermittent OCS use is associated with adverse outcomes; the events increase with increasing dose. Compared with non-OCS patients, the risk of experiencing any adverse outcomes was elevated for one-off OCS and increased with increasing frequent pattern of intermittent OCS prescribing.⁶⁰
- Whilst there are a paucity of data on the timing between OCS exposure and risk of AEs, it should be considered that the damage from most of the OCS-related chronic events and AEs as part of the OCS sub-model are irreversible, i.e. the co-morbid condition will not disappear or resolve itself upon a reduction/cessation of OCS (e.g. cataracts, cardiovascular disease, renal impairment etc.)
- In addition, there may be long-term cellular changes that occur with long-term OCS use. Genome wide association studies in COPD have identified that OCS use is associated with epigenetic modifications, namely methylation of CpG dinucleotides.⁶² It was found that CpG sites annotated to processes associated with clinically relevant side effects of OCS, such as hyperglycaemia/insulin resistance, weight gain, and osteoporosis were plausibly associated. This suggests that OCS have permanent effects on the genome, causing epigenetic modifications which could increase in frequency with cumulative OCS exposure, hence contributing to the risk of adverse events and the inability for these events to be stopped or reversed following discontinuation of OCS.

Section C: Textual clarification and additional points

C1. Table 40, page 89, CS Doc B

A column heading states 95% CI, but these data are not presented. Are the data presented standard errors?⁵

Yes, the column heading was mistakenly labelled as “95% CI” and should be “standard errors”. The 95% CI are presented below in Table 28.

Table 28: Inputs for mortality

Disease state	Mean	Lower CI	Upper CI	Source
SMR in remission (relative to general population)	■	■	■	CPRD ⁶³
SMR in stable disease (relative to general population)	■	■	■	
SMR in relapse (relative to general population)	■	■	■	

Abbreviations: SMR: Standardised mortality ratio; CI: confidence interval; CPRD: Clinical Practice Research Datalink

C2. Appendix D 1.1 Electronic databases

The search dates listed for the Cochrane Library are “1st May 2003 to 6th June 2003”. Please clarify whether the end date should read 6th June 2023 to align with other databases searched.¹

Yes, the end date was mistakenly written as “2003” and should be “2023”.

Appendix 1

This appendix presents a comprehensive overview of the approach adopted to inform transition probabilities in the economic model, by treatment arm.

Throughout this document, specific information pertaining to the below has been provided in response to some questions. The relevant questions are noted within the below explanations.

Benralizumab arm

Prior to the response assessment (Week 0 to Week 52)

- Transition probabilities in the benralizumab arm of the model were derived from all patients in the benralizumab arm of MANDARA up until the time of response assessment (Week 52).

Following the response assessment (Week 52 onwards)

- Patients who were identified as being responsive to benralizumab (defined as BVAS=0 and an OCS dose ≤ 4 mg/day) at Week 52 continued treatment; transition probabilities for responders were then informed only by the subgroup of responders in the benralizumab arm of MANDARA.
- It was assumed that responders' transition probabilities remained constant throughout the remainder of the lifetime horizon of the model. This assumption was consistent with the assumption of no treatment waning effect in the evaluation of benralizumab for severe eosinophilic asthma (TA565).¹⁸

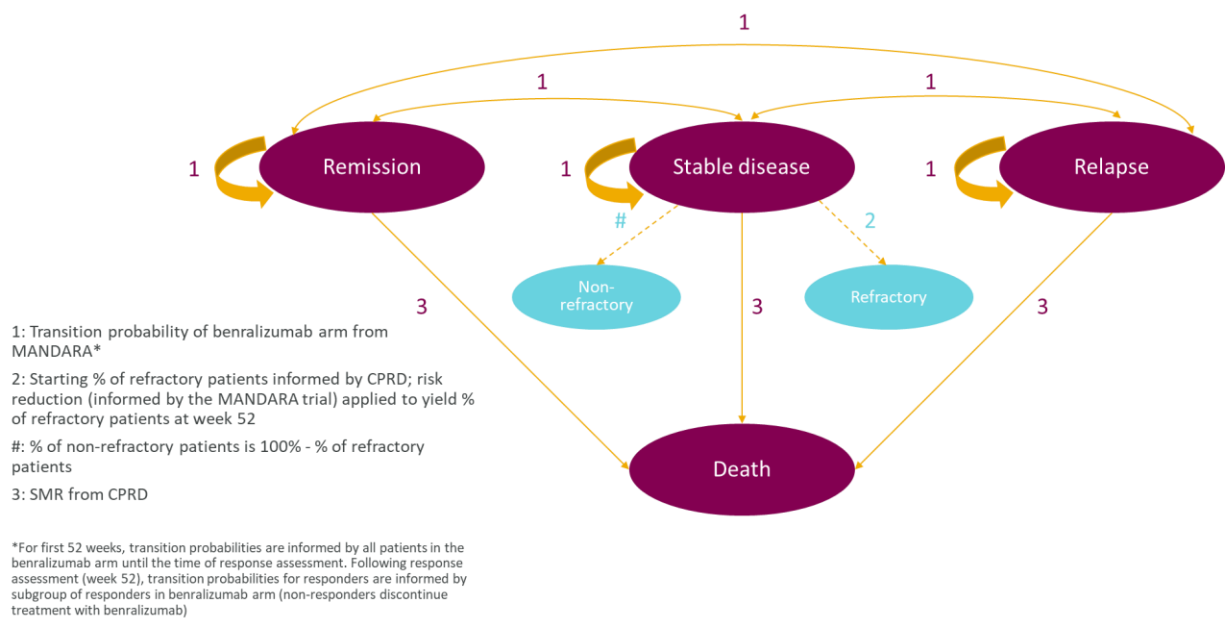
The dataset from MANDARA and model syntax used to estimate transition probabilities in the benralizumab arm are provided in response to question B5.

SoC arm (Week 0 onwards)

- In the absence of head-to-head clinical trials assessing the efficacy of benralizumab versus SoC in patients with EGPA, an ITC was conducted.
- The outcomes of the ITC were applied to the transition probabilities derived from all patients in the benralizumab arm of MANDARA to generate the transition probabilities for the SoC arm, as outlined in the response to question B.4 (a). The approach adopted and assumptions underpinning specific transition probabilities in the SoC arm (from stable disease to relapse and from relapse to stable disease) are outlined in the response to question B.1 (a).
- No response assessment was conducted for the SoC arm, in line with UK clinical practice. All patients who discontinued benralizumab at Week 52 received SoC and were subject to SoC transition probabilities.
- In the absence of evidence to suggest that transition probabilities change over time, transition probabilities for the SoC arm remained constant over the time horizon.

Figure 18 and Figure 7 [presented in the response to question B.1 (a)] illustrate key data inputs used to parameterise the model structure for the benralizumab arm and the SoC arm.

Figure 18: Model structure parameterisation, by treatment arm – benralizumab arm



Abbreviations: CPRD: Clinical Practice Research Datalink; SMR: standardised mortality ratio

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Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Patient Organisation Submission

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Vasculitis UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Vasculitis UK support patients with all types of vasculitis and their families by providing peer to peer support, information and advice. We support research in vasculitis and grant research awards annually. Our funds come from donations and bequests. We have had some honorariums from industry (Vifor pharma) for patient participation in panels.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	By communicating with patients. We have two big online groups with around 7,000 patients each and we run a helpline 7 days per week. We also meet patients face to face in local support group meetings. We have specifically asked for feedback from our members with EGPA

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	EGPA vasculitis is the rarest of the ANCA associated vasculitides and patients not only have asthma but also sinus and nose symptoms and may have a number of other symptoms including: rashes, nerve damage including pins and needles or numbness, bowel trouble and blood loss, anaemia, heart problems, muscle and joint pain and fatigue. A young adult patient told us: <i>EGPA is hard to live with, not just in terms of asthma but in the effect of quality of life when you are flaring and fatigue is something I find incapacitating, as well as the associated troubles like multiple chest infections.</i> Nerve and joint pain plus the respiratory issues caused by the asthma are factors that reduce mobility, and the risk of chest infections that increase with treatment increase isolation as patients shield to avoid getting infections. As EGPA is chronic, patients have to live with their illness and the damage caused by it prior treating it as well as damage caused by the treatment for ever. As flare ups and relapses are not uncommon, the burden of the illness is high. From a carer: <i>Our life has changed since the diagnosis. The side effects of the treatment were not easy to deal with – cyclo and steroids are horrific. My husband was given a new treatment as he had three severe exacerbations of asthma in a year, but although it was better he couldn't taper his steroids. Now waiting for him to have more than 4 exacerbations to be eligible for other treatment. What a life to live for him and for us. Wishing him to become more ill to get treatment to get better so our life together will get better. I am ashamed to admit it, but yes this is our reality.</i>

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Corticosteroids, cyclophosphamide and mycophenolate are the most common treatments our members have reported getting for their EGPA, then some get mepolizumab or benralizumab through asthma clinics. Patients believe that the available treatment is not always as effective as targeted therapy and have commented on the change in their lives with change of medication. Most concerns are about the long-term side effects from the treatment, but many have reported side effects of steroids. They have also reported that even though they get immunosuppressant as steroid sparing medication, they don't manage to get on very low dosage or successfully stop steroids. <i>" I was manic most of the time and found it difficult to focus. Work became very challenging and home life was tough on my wife having to deal with my mania, grouchiness caused by lack of sleep and I was ravenous all the time. "</i>
8. Is there an unmet need for patients with this condition?	Yes, there is. EGPA is rare but it can be severe, and the impact of the illness is high on the patient's life. Targeted therapy is needed and early intervention before severe damage is done is a must to improve outcomes and get patients in remission fast.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In general the EGPA patients who are on benralizumab through asthma clinics have only positive comments about it. It controls their EGPA and their asthma, they have less chest infections and they can taper their steroids successfully. They refer to it as life changing. Better quality of life, less hospital appointments, they can live a more normal life going to work etc. <i>Nothing is more powerful than patients talking from their heart so here are some quotes:</i> <i>"Benralizumab has been life changing for me, having multiple asthma attacks previously and needing high dose steroids for over a year to control the inflammation, I am now off steroids completely and my severe asthma due to egpa is really well managed with Benralizumab. It has meant I don't require stronger treatment such as cyclophosphamide."</i> <i>"Benralizumab has meant less chest infections, less asthma attacks and less mobility as I can go out and not be as worried about the cold air or petrol fumes/pollution affecting normal breathing."</i> <i>"I feel really grateful that benralizumab is now an option for egpa patients, especially as my first flare started at 24 in what they think was the second stage of egpa and my first egpa asthma attack aged 25, a drug like cyclophosphamide would have much more long term detrimental effects, in comparison."</i> <i>"Since Benralizumab my day to day is pretty normal..I still tire but am able to function at work and at home. In fact I almost forget about my condition at times but obviously reminded by the daily drugs."</i> <i>"Benra has been life changing for me. I can't say better than that. I am able to lead a normal life. Work and home life is better. My asthma is under control. I doubt that I would be able to work if I had to rely on pred."</i>

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None of our members responded negatively about taking the certain medication, but as in all medications there will be patients experiencing some side effects, or patients the medication doesn't work for. As said, we haven't had any negative feedback although we specifically asked for both positive and negative feedback. <i>"I cant think of any disadvantages"</i> said one of our members.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We believe that all patients with severe EGPA would benefit.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	EGPA is rare, EGPA can be severe, EGPA is chronic. At the moment to be treated with benralizumab you have to be lucky to be looked after by a hospital that can prescribe it through their respiratory clinic. It is a postcode lottery that creates an inequality of care to these patients. Not all EGPA patients are looked after in asthma clinics, and some get there after being treated unsuccessfully for their EGPA. <i>“ I then started at the asthma clinic..” (6 months after diagnosis and not responding in two immunosuppressants plus steroids – now on benralizumab)</i> <i>“ I moved to Liverpool just before my flare, which was very lucky, as I found after it's one of the few specialist centres to prescribe benralizumab in the country. My own local hospital, for instance, does not use it as far as I am aware. I was just very lucky to be living at the right place at the right time, for the right treatment.”</i>

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• There is need of targeted therapy to treat EGPA patients • Treatment should be accessible to all EGPA patients – not depending on where they live • Early treatment is essential, EGPA patients don't only have asthma to deal with. • Quality of life is important and the ability to work is significant to patients •

Thank you for your time.

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Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Professional organisation submission

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

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

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

Information on completing this submission

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

About you

1. Your name	██████████
2. Name of organisation	I work for the severe asthma service based at MFT and am commenting on behalf of the Association of Respiratory Nurses (ARNs)
3. Job title or position	██████████
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes (nurses) A specialist in the treatment of people with this condition? No (Whilst we see patients with this disease in our clinic, due to the small proportion of people which this disease affects, I would not define myself as specialist but as someone who has some experience as part of an MDT in managing this disease). A specialist in the clinical evidence base for this condition or technology? No
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses is a not for profit organisation and professional forum for respiratory nurses.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer,	Yes - AstraZeneca £61,825.00 – Yearly corporate partnership with ARNS and evening symposium session at ARNS Conference 2024

amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To gain better control the disease and aim to reduce the oral corticosteroid burden of current therapy
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Disease remission and oral corticosteroid burden reduction.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Due to the multi system impact of this disease, there needs to be a joined up approach in the assessment, management and treatment of all specialities involved in caring for this cohort, ther also nationally needs to be greater education in regards to diagnosis and management. From a patient perspective there needs to be better support mechanisms insitu such as patient support groups

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently EGPA in our experience has historically been treat with DMARDs and oral/IV corticosteroids. In our severe asthma service Benralizumab can only be prescribed if a confirmed asthma diagnosis in proven and insitu and is prescribed upon asthma licensing
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Rheumatology RE ANCA-associated vasculitis UK guidelines are currently being revised. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis was recently published in nature in 2023
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	From anecdotal observation I think care can vary across the UK secondary to limited knowledge re the disease area. These patients need to be assessed and managed in specialist care.
9c. What impact would the technology have on the current pathway of care?	Unsure
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Unsure
10a. How does healthcare resource use differ between the technology and current care?	In our severe asthma service Benralizumab can only currently be prescribed if a confirmed asthma diagnosis in proven and insitu
10b. In what clinical setting should the technology be used? (For example,	Specialist clinics with knowledge surrounding the disease and management

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Greater training and education, as per earlier comments this is a rare disease area with limited knowledge within healthcare re diagnosis and management, furthermore additional staff and facilities to deliver and monitor this will be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	If this is successful in reducing OCS burden then possibly, however close monitoring of all body systems and disease activity will require close observation
11a. Do you expect the technology to increase length of life more than current care?	If this is successful in reducing OCS burden then possibly, however close monitoring of all body systems and disease activity will require close observation
11b. Do you expect the technology to increase health-related quality of life more than current care?	If this is successful in reducing OCS burden then possibly, however close monitoring of all body systems and disease activity will require close observation
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Unsure

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Patients will require close clinical observation to assess for and monitor for any signs of underlying disease activity across all body systems effected by EGPA
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Unsure
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	If this treatment can be delivered in a specialist centre by clinicians and healthcare professionals experienced in the care and management of this disease then I think it will make a huge improvement patient quality of life.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Unsure
16a. Is the technology a 'step-change' in the management of the condition?	Unsure
16b. Does the use of the technology address any particular unmet need of the patient population?	Unsure
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	From anecdotal observation of clinical practice using Benralizumab, we have seen little in the way of adverse effects and side effects of Benralizumab, however have seen significant patient harm secondary to the long term side effects of oral corticosteroids from both a physical, psychological perspective.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	/

18a. If not, how could the results be extrapolated to the UK setting?	/
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	/
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	//
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	/
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	/
20. How do data on real-world experience compare with the trial data?	/

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	We need to ensure that there is equity of care in delivery of this Tx to patients if approved.
21b. Consider whether these issues are different from issues with current care and why.	/

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• EGPA is a rare disease requiring greater investment in care and Tx to reduce OCS burden and improve patient related quality of life and OCS related side effects • If Benralizumab is approved for the Tx of EGPA then we recommend initiation only by specialists involved in the care and management of this disease with close management of the patient to observe for any underlying signs of vasculitis flare across all organs which EGPA can impact upon • • •

Thank you for your time.

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Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Professional organisation submission

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

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

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

Information on completing this submission

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

About you

1. Your name	██████████
2. Name of organisation	British Society for Rheumatology
3. Job title or position	██████████
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? ~~Yes~~ or No • A specialist in the treatment of people with this condition? ~~Yes~~ or No • A specialist in the clinical evidence base for this condition or technology? ~~Yes~~ or No • Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society for Rheumatology is the leading UK specialist medical society for rheumatology and musculoskeletal care professionals. We are funded by our membership as well as other commercial activities such as the sale of our journals, through our events and education programmes and by running our clinical registers. We also receive event sponsorship from pharmaceutical companies as set out in the Disclosure UK database https://www.abpi.org.uk/reputation/disclosure-uk/
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	The BSR has had one Astra Zeneca funded journal project in the last 12 months. This was a grant of £31,000 for a virtual roundtable, video and accompanying journal article on access to care for systemic lupus erythematosus patients worldwide.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To stop progression of disease and morbidity. • To induce and maintain remission. • Reduce burden/toxicity of other treatments i.e. steroids which can have adverse side effects.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Maintaining clinical remission, whilst achieving a meaningful reduction in steroid dose and stopping steroids if possible. • EULAR definition of remission - BVAS of 0, glucocorticoid dose ≤ 7.5 mg/day. However, most clinicians would advocate for doses lower than this wherever possible, noting there is no real 'safe' dose of steroid. The 2018 EULAR taskforce agreed that the risk of harm at dosages of >10 mg/day is elevated. For dosages between >5 and ≤ 10 mg/day, patient-specific characteristics determine the risk of harm. For doses <5 mg the risk was considered low, but not zero. Ref: Buttgereit F SP0160 2018 EULAR recommendations for the use of glucocorticoid therapy Annals of the Rheumatic Diseases 2018;77:42.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients may present to ENT, chest medicine, rheumatology, clinical immunology, neurology, cardiology. The diagnosis is usually delayed because of the different ways in which the condition can present. After the inevitable delay in diagnosis, there is a wide heterogeneity in the ways that different units treat this condition. Some clinicians only use corticosteroids, while some use less powerful immunosuppressive agents like methotrexate or mycophenolate mofetil. The international recommendations are to treat with intravenous cyclophosphamide and yet this may be a problem because not all units may have access to infusion suites. For patients with relapsing disease, (almost every single patient will relapse eventually), the choice is with Rituximab. The evidence base is not great for this drug, and neither is the confidence in the academic community. Especially, for ANCA negative EGPA, this is not thought to be a great option. This means overuse and abuse of corticosteroids, with the inevitable side effects of corticosteroid therapy. Remission maintenance is typically with Methotrexate or Azathioprine. Relapse on one of these maintenance agents would require increases in steroid dosing as well as considering repeat rounds of remission induction. Currently IL5 inhibition is not available in the UK specifically for EGPA (NICE TA845), but it is sometimes accessed for patients who also meet the criteria for severe eosinophilic asthma (NICE TA671), where a choice from Mepolizumab, Benralizumab or Reslizumab is available.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, Luqmani R, Mills J, Mooney J, Venning M, Watts RA; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford). 2014 Dec;53(12):2306-9. 2. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, Holle JU, Hollinger N, Karadag O, Kronbichler A, Little MA, Luqmani RA, Mahr A, Merkel PA, Mohammad AJ, Monti S, Mukhtyar CB, Musial J, Price-Kuehne F, Segelmark M, Teng YKO, Terrier B, Tomasson G, Vaglio A, Vassilopoulos D, Verhoeven P, Jayne D. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024 Jan 2;83(1):30-47.

	The second guideline (2 above) is the most recent, from the European Alliance of Associations for Rheumatology (EULAR). Separate recommendations for EGPA were included in this update, including the use of IL5 inhibition (Mepolizumab). This is not available specifically for EGPA in the UK according to NICE guidance (NICE TA845), but it is sometimes accessed for patients who also meet the criteria for severe eosinophilic asthma (NICE TA671), where a choice from Mepolizumab, Benralizumab or Reslizumab is available. IL5 inhibition is recommended by EULAR as first line for remission induction in non-organ/life threatening disease. Previous BSR guidelines (1 above) are now 10 years old and currently under revision. They talk about the management of ANCA associated vasculitis more generally rather than singling out EGPA for special mention. They were written before the use of IL5 inhibition in severe asthma was routinely introduced.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathways should be well-defined, but often they are not. There are recommendations that are based on evidence and the consensus views of clinicians who are experts in this condition. However, the reality of how these recommendations are put into practice is often based on the practical availability of services. This is not a common condition and therefore it is difficult for smaller centres to dedicate resources in the form of multi-disciplinary services, infusion suites, etc. So, there isn't a difference of opinion amongst the opinion leaders, but this does not necessarily lend itself to homogenous practices when faced with a rare condition which needs a lot of resource. In practice, the pathway to access IL5 inhibition for EGPA patients currently relies on specialist Respiratory input, which is variable in the UK. It is possible some EGPA patients would not meet the respiratory criteria, especially if their relapse is in a different domain.
9c. What impact would the technology have on the current pathway of care?	If approved for use, Benralizumab would be the first drug that would be tailor made for EGPA and would most certainly reduce hospital attendances, out-patient clinic use - and most importantly – corticosteroid side effects in the long-term which will have incalculable benefits to the NHS health economy aside from the individual benefits to patients. Its use would standardise pathways and equity of access to IL5 inhibition for patients with EGPA.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not entirely – it would also allow Rheumatologists to recommend initiation in refractory patients, currently accessed through Respiratory services only and for qualifying patients.

10a. How does healthcare resource use differ between the technology and current care?	Current treatment options for treating new or relapsing EGPA include intravenous infusion therapies only. They in turn need access to infusion suites, dedicated infusion nurses etc. That is a huge resource. Benralizumab is a subcutaneous injection and does not need hospital resources for delivery.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist out-patient vasculitis clinics or at their recommendation through MDT.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It will be important to ensure that there is an adequate programme for teaching patients how to use and dispose of the injections. However, generally, this will exist in every rheumatology department and will need <u>minimal resources</u> to tweak.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes – would only be used in relapsing or refractory patients in whom current UK standard of care was not sufficient.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – would only be used in relapsing or refractory patients in whom current UK standard of care was not sufficient.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Young women. Cyclophosphamide is thought to reduce fertility, and most clinicians would avoid prescribing Rituximab in pregnancy. Benralizumab may be a safer option in young women.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will be easier for healthcare professionals, as this would allow rheumatologists to recommend initiation in refractory patients, currently accessed through Respiratory if patients also meet the criteria for severe asthma (TA565).
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There should be rules – The diagnosis of EGPA should be made objectively and, as per EULAR recommendations, initiation would be recommended for use in relapsing/refractory cases. (Hellmich B, et al. Ann Rheum Dis 2024;83:30–47. doi:10.1136/ard-2022-223764). There should be quantification of the disease activity using standard clinical tools and the drug should only be used when there is objective evidence of disease. At 6 months, it should be possible to demonstrate absence of disease using standard clinical tools. We should be able to demonstrate reduction of prednisolone use. No additional tests are necessary – the above should be standard care for all vasculitis.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, the reduction of corticosteroid use will most definitely improve Health-related quality of life (HRQOL), but that will be difficult to quantify.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – we already know this treatment works for a proportion of patients with refractory/relapsing EGPA, but currently can only be accessed through Respiratory services. This appraisal would allow vasculitis services to initiate treatment in a timelier fashion. Also, this is a novel way of targeting the disease. Improvements in targeted drug delivery will be able to improve the way we treat this and other autoimmune diseases.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – there are currently no disease specific treatments in use for EGPA. This would be a first. The other drugs used are extrapolations of evidence from their use in other forms of vasculitis. It would also allow Rheumatologists to recommend initiation in refractory patients, currently accessed through Respiratory only for qualifying patients.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects as listed in the BNF are not particularly severe. Post-marketing surveillance may tell us more, but at present there is no major safety signal. In addition, the head-to-head study of Benralizumab with Mepolizumab had a very similar and acceptable safety profile. No patient in the Benralizumab group experienced an adverse event significant enough to require discontinuation. (Wechsler et al. NEJM 2024;390:911-21).

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The only study of note is the MANDARA trial (Wechsler et al. NEJM 2024;390:911-21), a head-to-head study of Benralizumab and Mepolizumab. This was a non-inferiority study. The primary endpoint was remission at 36 and 48 weeks (defined as a BVAS of 0 on glucocorticoids $\leq$ 4mg per day). Benralizumab was found to be non-inferior, but not superior to Mepolizumab. The improvements seen were modest. This appears to have been a problem with study design, rather than drug effectiveness. Entry criteria allowed for patients to already have a remission BVAS score of 0, which applied to 49% and 47 % of the Benralizumab and Mepolizumab groups respectively at baseline. This improved to 59% and 56% respectively at 48 weeks. The minimum dose of steroids for entry to the study was 7.5 mg per day, regardless of the reason for administration. It is therefore possible that patients were taking steroids for reasons other than EGPA, which would skew the data. This also meant the mean steroid dose was only reduced by 8.04 mg by the end of the study (11.02 +/- 5.25 mg at baseline, versus 2.98 +/- 3.76 mg at week 48). In real clinical practice, patients being considered for this drug will have active disease (BVAS >0) and are likely to be on steroid doses more than 7.5 mg per day to acutely control relapse.
18a. If not, how could the results be extrapolated to the UK setting?	The potential gains for appropriately selected patients are likely to be greater than seen in the MANDARA study due to the problems with study design, as mentioned above (Item 18).
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – even for patients entering the trial already in remission (BVAS = 0), maintaining this whilst achieving clinically meaningful steroid dose reduction is important to prevent long term cumulative glucocorticoid toxicity.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	We have not been able to use it, so unable to comment on this.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Women are disproportionately affected; Younger women of childbearing age are the main demographic.
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• IL5 inhibition is an important aspect of care in EGPA. This is formally recognised by European colleagues in their guidelines, but not currently recognised by NICE. Patients in the UK are potentially at a disadvantage with regards treatment options. • There is clinical trial evidence that it will both help a small number of patients in inducing remission and that it will help to reduce the cumulative glucocorticoid dose. • The subcutaneous route is an improvement over the only two other drugs that are currently use for remission/ induction – cyclophosphamide and Rituximab. • Real benefit for the main demographic of EGPA – women of child-bearing age. • Although Bendralizumab could be accessed via Respiratory colleagues, there is a chance some patients would not meet their prescription criteria, especially if relapsing in a non-respiratory domain. This would disadvantage some patients with EGPA.

Thank you for your time.

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Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	████████████████████
2. Name of organisation	UK Kidney Association
3. Job title or position	██████████ ██████████
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	We have received £141,000 from AZ in 12 months- this is for sponsorship, grants and membership.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To induce and maintain disease remission, with the aim of • Reducing symptom burden • Improving quality of life • Preventing accrual of disease-related chronic organ damage (in particular, cardiomyopathy, airway remodelling, chronic kidney disease, neuropathy) • Whilst minimising treatment-related side effects and damage
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	More time spent in remission and prevention of disease flares. Reduced glucocorticoid usage and related toxicity. Reduced emergency and unplanned care.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are no licensed therapies for EGPA available in the UK (except for patients who qualify for biologic therapy via severe asthma pathways). There is scant evidence for the efficacy of alternative (unlicensed) therapies that are commonly used in conjunction with glucocorticoids in UK practice, such as conventional synthetic DMARDS (mycophenolate mofetil (MMF), azathioprine and methotrexate) and rituximab. Proven, effective therapies are needed. We recognise that glucocorticoid dependency is very common in EGPA, and that this is associated with significant toxicity including mood and sleep disturbance, cardiovascular disease, metabolic disorders including diabetes, osteoporosis, cataract formation etc. Alternative treatments that can reduce glucocorticoid use and toxicity are a priority in this patient group. Unrelated to therapy, unmet needs include diagnostic delay, and access to expert and unified multidisciplinary care.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In the UK, EGPA (once diagnosed) is exclusively managed in secondary care; often but not always in specialist respiratory or vasculitis (rheumatology/renal) services. First-line treatment is with glucocorticoids. In patients with relapsing or steroid-dependent disease, conventional DMARDS (e.g. MMF, azathioprine, methotrexate) are often used in attempt to lower glucocorticoid burden and to reduce relapse risk, though there are very limited controlled data for their efficacy to support this approach. In patients with severe disease manifestations, remission-induction treatment with cyclophosphamide and/or rituximab (using protocols established in RCT for other forms of systemic vasculitis) are often used, though patients with EGPA were not specifically included in many of these studies. None of these therapies are licenced in EGPA. More recently, patients with severe asthma as a manifestation of EGPA may receive anti-IL5 therapy (e.g mepolizumab, benralizumab) or other biologics (e.g. tezepelumab) via existing commissioned routes in specialist severe asthma services.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Evidenced-based consensus recommendations for treatment of EGPA include: American College of Rheumatology: https://pubmed.ncbi.nlm.nih.gov/34235894/ European Alliance of Associations for Rheumatology: https://pubmed.ncbi.nlm.nih.gov/36927642/ European EGPA Study Group: https://pubmed.ncbi.nlm.nih.gov/37161084/ The British Society of Rheumatology will soon publish an updated management guideline (to be endorsed by the UK Kidney Association) for patients with ANCA-associated vasculitis including EGPA (expected Q1 2025) Importantly, all these guidelines recommend anti-IL5 therapies in the treatment of EGPA.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is poorly defined in many regions. Diagnostic delay is common – owing to disease rarity, heterogenous presentation, spectrum of differential diagnoses and failure to recognise. Patients may initially present to primary care or acutely to emergency services. They may then be referred to a variety of secondary services (including respiratory medicine, rheumatology, nephrology, neurology, ENT surgery) depending on clinical phenotype and local expertise / service set up. Long-term follow up may continue with any of these specialities and is commonly lead by rheumatologists and renal physicians with experience in managing other forms of vasculitis (such as GPA & MPA). We know that access to specialist centres and MDT care is associated with better outcomes (e.g https://pubmed.ncbi.nlm.nih.gov/38782514/) but that such services are not well developed in all regions, and that

	many patients are managed in general renal/rheumatology services. The upcoming BSR/UKKA management recommendations for AAV including EGPA highlight the importance of specialist MDT care and will recommend that all patients have access to this.
9c. What impact would the technology have on the current pathway of care?	We propose that access to benralizumab for EGPA should be under guidance the of established MDTs for vasculitis and related diseases, usually within renal and rheumatology departments. These existing MDTs include multi-speciality clinical expertise, with pharmacy and specialist nursing support, and have experience in the management of patients with other forms of vasculitis requiring commissioned therapies (e.g. avacopan in AAV, tocilizumab in GCA). The introduction of benralizumab is therefore likely to improve the care pathway, as patients will have MDT referral for both diagnostic review and consideration of treatment eligibility, thus improving equity of access for patients and patient outcomes. We anticipate that approval of a new class of treatment may raise awareness of disease and possibly reduce diagnostic delays.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Patients with severe asthma as a manifestation of EGPA may already receive benralizumab via existing commissioned routes in specialist asthma services. Patients with asthma who do not meet severity criteria for biologic therapy, even if severe non-asthma manifestations of EGPA are present (e.g., cardiomyopathy, neuropathy, kidney disease etc) do not currently have access to this evidence-based treatment. Beyond severe asthma pathways, the therapy is not in currently in use for treatment of EGPA in the NHS.
10a. How does healthcare resource use differ between the technology and current care?	Care for EPGA will remain in secondary care, and the introduction of this therapy is likely to increase patient access to dedicated MDT review. Therapy can be self-administered at home, so unlikely to increase demand for day-case care. No specific blood monitoring is required for benralizumab; indeed, in comparison with conventional DMARDS and cyclophosphamide the requirement for monitoring blood tests is likely to be reduced. Likely to reduce emergency and unplanned care due to reduction in flare rate and glucocorticoid complications.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (with specialist MDT oversight) and specialist clinics, including multi-disciplinary vasculitis clinics.
10c. What investment is needed to introduce the technology? (For example,	No additional facilities or equipment needed. Therapy can be delivered and self-administered at home using existing pharmacy pathways.

for facilities, equipment, or training.)	Some additional training (nursing, pharmacy, patients) may be required as the treatment is introduced to clinical practice, although existing renal, rheumatology and vasculitis clinics will be experienced in using similar biologic treatments.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – RCT and observational studies demonstrate significant glucocorticoid sparing potential, and high rates of (often glucocorticoid free) clinical remission – areas of unmet need and clinical priority as highlighted above.
11a. Do you expect the technology to increase length of life more than current care?	Yes. The FFS (five factor score) is predictive of mortality in EGPA and includes renal insufficiency (serum creatinine >1.58 mg/dl), proteinuria >1 g per day, cardiomyopathy, gastrointestinal involvement, and central nervous system (CNS) involvement. Patients with these disease features (in the absence severe asthma manifestations) do not currently have access to anti-IL5 therapy in the UK. Cardiovascular disease is the leading cause of death (>30%) in EGPA long-term, likely due to both disease and treatment-related complications. Glucocorticoids contribute to this risk - evidence in other autoimmune rheumatic disorders show a dose-dependent increased risk of MI, stroke, and death, even at doses ≤5 mg/day. Thus, the ability to reduce / withdraw glucocorticoids with benralizumab treatment (in proportions reported in the MANDARA study) is very likely to reduce long-term cardiovascular risk and associated mortality (although not captured during the short-term trial follow up).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Unrelated to asthma manifestations, patients with EGPA experience high symptom burden due to multisystem nature of disease – chronic rhinosinusitis, debilitating neuropathy, and symptoms related to cardiac failure are particularly challenging. This is compounded by the burden of symptoms accrued as a result of glucocorticoid toxicity – diabetes, osteoporosis and fracture risk, mood disturbance, cataracts, weight gain etc. Access to a proven therapy that increases periods of disease-free remission and glucocorticoid reduction will have a significant and long-term impact on quality of life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	RCT evidence supports use of benralizumab in relapsing or glucocorticoid-dependent EGPA. Whilst not the subject of clinical studies thus far, we anticipate that newly presenting patients should also benefit from treatment, as risk of mortality and glucocorticoid use/dose are greatest during the first few months after diagnosis.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Therapy is administered by a subcutaneous auto-injector, acceptable to nearly all patients. No additional blood monitoring is required during benralizumab treatment. Observational data suggests treatment with benralizumab permits withdrawal of oral immunosuppressants in a significant proportion (>25%) of patients. This will reduce both treatment-related adverse events and the requirement for regular blood test monitoring (as is required with conventional DMARDs, cyclophosphamide etc)
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We propose that Benralizumab for EGPA patients should be assessed, discussed and managed by established specialist renal/rheumatology/vasculitis MDTs, that already have expertise in the multi-system nature of EGPA and the infrastructure and experience in biologics in other forms of vasculitis. We propose at least annual review by the MDT to review treatment efficacy (relating to disease activity, flare rate, glucocorticoid tapering, withdrawal of other immunosuppressive agents) and to determine duration of ongoing treatment. Potential indications to stop treatment may include failure to reduce flares, failure to taper glucocorticoids or other treatments. We would support a requirement to collect real-world outcome data of patients treated with the technology for EGPA, relating to both efficacy and safety both in the short term, and longer term, beyond one year.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No – it is anticipated that health related benefits will be captured in the QALY calculation
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the technology is innovative – potentially the first targeted anti-cytokine therapy to be recommended for treatment of EGPA in the UK, with RCT and high-quality observational data to support its use. The only other therapy supported by RCT evidence in EGPA is cyclophosphamide, which is usually reserved for life- or organ-threatening disease and associated with significant toxicity.
16a. Is the technology a 'step-change' in the management of the condition?	Absolutely – it would provide access to the first licensed therapy supported by high-quality randomised trial data for treatment of EGPA in the UK
16b. Does the use of the technology address any particular unmet need of the patient population?	Evidence indicates that benralizumab treatment extends periods of disease-free remission and permits glucocorticoid reduction and withdrawal, clear areas of unmet need in management of this disease.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment is well tolerated. We are not aware of any long-term safety issues in patients already treated for severe asthma with this therapy.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In the MANDARA study, the comparator treatment to Benralizumab was Mepolizumab; Mepolizumab is not commissioned for EGPA in the UK but was demonstrated to be effective in the MIRRA study.
18a. If not, how could the results be extrapolated to the UK setting?	Placebo-treated patients in the MIRRA study more likely to represent the current UK population treated with standard care in EGPA.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Sustained disease remission, glucocorticoid-minimisation, and quality of life – addressed in RCT and observational data. Survival – not primarily addressed in relatively short-term trial follow up.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Evidence in other, comparable, autoimmune rheumatic diseases shows that glucocorticoid dose and duration associates with development of cardiovascular disease and with mortality. Whilst specific data are lacking (largely due to disease rarity), we would expect this to hold in EGPA, and that reduction in glucocorticoid use would associate with reduced cardiovascular risk and improved survival in this patient group.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Published observational and ‘real-world’ data replicate RCT findings – with greater time spent in remission, reductions in glucocorticoid dose, increased glucocorticoid withdrawal, and ability to withdraw other immunosuppressive agents.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to Specialist Care: patients in underserved or rural areas may lack access to specialist services, which could limit equitable access to new therapies like benralizumab. Socioeconomic Disparities: self-administration of benralizumab at home may require additional patient education and training. Factors such as education level, healthcare literacy, housing stability, and access to healthcare resources could affect patients' ability to manage the treatment effectively. Cultural and Language Barriers: For patients from non-English-speaking or diverse cultural backgrounds, effective communication about disease management, self-administration, and potential side effects may require tailored support. The introduction of benralizumab may highlight the need for clearer, standardized pathways to ensure all eligible patients - regardless of location, clinician expertise, or health system constraints - can access this treatment.
21b. Consider whether these issues are different from issues with current care and why.	No - these issues are common with other therapies used for EGPA and complex multi-system immune disorders in general. The potential approval of a therapy specifically for EGPA will focus attention on the condition, and may lend weight to addressing these equity issues more broadly.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• EGPA is a rare disease, and patients face significant unmet needs, including diagnostic delays, glucocorticoid-dependence (with resultant toxicities) and a lack of other proven or licensed therapies, making effective alternatives like benralizumab highly desirable. • Benralizumab demonstrates significant benefits in randomized trials and real-world studies, including increased remission rates, reduced relapse risk, and glucocorticoid-sparing effects, which are priorities for improving patient outcomes. • Benralizumab represents a groundbreaking, targeted treatment for EGPA, offering a safer and more effective alternative to conventional, less-proven, therapies like cyclophosphamide and synthetic DMARDs. • The therapy's subcutaneous administration allows for at-home use, minimal additional resource requirements, and its introduction has the potential to reduce emergency and unplanned care, while promoting referral to specialist MDTs for improved disease management. • Endorsed by international guidelines (e.g., EULAR, ACR, upcoming British Society of Rheumatology/UK Kidney Association recommendations), access to benralizumab would address critical gaps in EGPA management and aligns with best practices in vasculitis care worldwide.

Thank you for your time.

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Professional organisation submission

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

12 of 12

Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Professional organisation submission

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

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

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

Information on completing this submission

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

About you

1. Your name	[REDACTED]
2. Name of organisation	UKIVAS (UK and Ireland Vasculitis Rare Disease Group)
3. Job title or position	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKIVAS society brings together clinicians, researchers, allied health professional and patients with a clinical and research interest in improving outcomes for people with systemic vasculitis in the UK. We are particularly interested in improving access to targeted treatment in EGPA, in order to reduce the frequency of flares and reliance on high dose glucocorticoids – and thereby improve disease control, reduce adverse effects and have a positive impact on health-related quality of life. Our two co-chairs from rheumatology and renal specialities represent our multidisciplinary working, we also have specialists from ENT, Respiratory, Neurology, and Cardiology within our membership. Our UKIVAS members email list includes >80 NHS research sites across the UK, resulting in direct contact with clinicians, patients, nurses and allied health professionals working within clinical practice, trials and research within the systemic vasculitides. We work with patient partners to ensure their voice runs through all aspects of UKIVAS work. The UKIVAS registry is supported via the NIHR portfolio in terms of patient recruitment. Support for educational meetings and previous investigator led research projects (not within EGPA) have been given by pharmaceutical companies including Vifor Pharma.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of treatment is to treat active refractory or relapsing active EGPA • To treat acute active symptoms of EGPA • To reduce number of disease relapses requiring escalation of glucocorticoid treatment • To reduce overall cumulative glucocorticoid burden Thereby reducing irreversible damage from: • Damage due to active EGPA (damage to lungs, sinuses, kidney and heart failure and valvular damage, skin ulceration and peripheral neuropathy) • Damage from prolonged moderate- high dose glucocorticoids or frequent escalation to high-dose courses of glucocorticoids for flares (risk of diabetes, hypertension, osteoporosis and fracture, infection, impact on mood, sleep appearance and weight change). Thereby reducing the impact of EGPA and its treatment on patient health- related quality of life. Also reducing the number of A&E attendances, acute hospital admissions and reviews in urgent outpatient clinics required, through reduction in number of people with flares of their EGPA requiring emergency treatment.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in number of flares of EGPA exacerbations Reduced cumulative glucocorticoid burden.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The ANCA-associated vasculitides (AAVs) encompass three conditions: Eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). Until recently, trials for the AAVs have focused on patients with GPA and MPA and treatment regimens for EGPA have been extrapolated from this evidence. For the first time, there is now evidence that targeted therapy with anti-IL5 medication is effective and very well tolerated in EGPA; with minimal side effects and no requirement for intensive blood monitoring. This technological appraisal- Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis- was discussed at the UKIVAS steering group meeting (comprising rheumatologists, nephrologists, nurse specialists and patient charity representative) in Birmingham on 26th November 2024, held at our annual educational meeting. This UKIVAS steering group gives full support to this TA. There is a clear unmet need in terms of treatment for patients with EGPA who can have a range of disease manifestations (lung, cardiac, neuro, skin, haematological and renal involvement). At present, the mainstay of treatment is with high dose glucocorticoids, non-specific disease modifying (DMARD) medications such as methotrexate, azathioprine or mycophenolate for “non-severe” disease, or cyclophosphamide (a chemotherapy agent) for severe manifestations. Non-specific DMARDs and cyclophosphamide have significant adverse effects including liver and blood count abnormalities, increased risk of infection and can impact on fertility and risk of malignancy. The cost (in terms of money and patient and healthcare time for blood monitoring and infusion delivery) is higher for DMARDs and cyclophosphamide than Benralizumab, which is self-administered by subcutaneous injection. The impact of disease activity, dealing with flares and subsequent increases in steroid dosages can also significantly impact on patients’ health-related quality of life. Glucocorticoids are effective short term in EGPA but can lead to a range of adverse effects and specifically worsen health related quality of life. Patients experience relapse frequently on steroid reduction in EGPA, with more than 80% of patients in real world data sets having at least one relapse and 20% experiencing severe (organ or life threatening) relapse. Bell et al Cureus 2023. Patients with EGPA here describe their experience with glucocorticoids during acute flares of EGPA: “when my steroids are high... I’m taking, well for me say about 30 mg a day, I get a kind of a depression almost. And it’s almost like - Well why should I bother getting up? (53-year-old female, EGPA, UK)”

“My worst worry is about that prednisone, because right now it is not too bad, I am not too old, but I am pretty sure I am not able to use 25 mg of prednisone for the rest of my life, because something else is going to go (47-year-old male, EGPA, Canada)”.

Trial data for Benralizumab show a reduction in relapse rates to approximately a third, with a 50% reduction in cumulative glucocorticoid dosages and 40% steroid withdrawal over 36 weeks. Despite inclusion of people with a range of disease manifestations of EGPA within successful clinical trials– including patients with asthma, neuropathy, sinonasal disease, cardiomyopathy, glomerulonephritis, and skin purpura- currently within the NHS, only patients with one type of EGPA presentation, that of acute severe asthma, qualify for treatment with benralizumab via asthma pathways.

There is also currently no facility for specialist rheumatology or nephrology MDTs to provide appropriate treatment with IL5 medications for any aspect of EGPA, despite the multi-organ nature of EGPA being managed by these teams. Such patients need to be referred onto severe asthma services to access IL-5 treatment. This situation is an anomaly in comparison with biologic therapy for all other forms of systemic vasculitis (e.g. Avacopan or Rituximab for ANCA associated vasculitis or Tocilizumab for giant cell arteritis) whereby specialist MDT teams within Rheumatology and Nephrology routinely manage these conditions.

This means that patients with EGPA are likely to be suffering potentially avoidable delays in appropriate treatment in the case of asthma manifestations, and potentially less effective treatment in the case of people without severe asthma manifestations, who do not qualify under the severe asthma inclusion criteria.

In clinical practice this leads to multiple flares of EGPA disease activity, requiring high dose steroid rescue courses and accumulated burden from glucocorticoid adverse effects.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Within the UK, EGPA is currently treated by different specialities depending on disease manifestation. Rheumatology departments and MDTs commonly diagnose and treat multisystem autoimmune disease including EGPA vasculitis. Vasculitis MDTs led by renal physicians (such as in Cambridge) can also manage and treat all forms of vasculitis, so would also manage EGPA. Other specialists will be involved depending on disease manifestation and severity including ENT, cardiology, dermatology, neurology, and respiratory, ideally within the context of a multidisciplinary team. In some cases, patients may be diagnosed via acute severe asthma pathways and then referred to rheumatology/renal services for treatment of their wider EGPA vasculitis. First line treatment is with glucocorticoids and DMARDS such as methotrexate, mycophenolate or azathioprine. In severe manifestations (cardiac, glomerulonephritis or neurological manifestations), cyclophosphamide or Rituximab are used for remission induction. These treatments are not licenced for EGPA and their use is mainly extrapolated from other types of ANCA associated vasculitis trials and recommendations. More recently, patients with severe asthma as a manifestation of EGPA may receive anti-IL5 therapy (e.g mepolizumab, benralizumab) or other biologics (e.g. Tezepelumab) via existing commissioned routes in specialist severe asthma services. We do note though that the recommended dosage of Benralizumab under the TA565 for use of severe eosinophilic asthma, is 30 mg every 4 weeks for the first 3 doses then every 8 weeks; whilst the trial data for Beralizumab in EGPA refers to 30mg every 4 weeks continuously. The panel may therefore want to consider the choice of dosage appropriate for EGPA.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	All current evidenced-based consensus recommendations now advocate use of anti-IL5 therapies in the management EGPA: The British Society of Rheumatology will soon publish and updated management guideline for patients with ANCA-associated vasculitis including EGPA (expected Q1 2025) American College of Rheumatology: https://pubmed.ncbi.nlm.nih.gov/34235894/ European Alliance of Associations for Rheumatology: https://pubmed.ncbi.nlm.nih.gov/36927642/ European EGPA Study Group: https://pubmed.ncbi.nlm.nih.gov/37161084/

Professional organisation submission

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

8 of 18

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Care pathways for EGPA depend on the method of presentation and disease manifestations, which are highly variable. Patients can present with a range of different symptoms and there can be significant delay in diagnosis in primary and secondary care, partly due to difficulties in differentiating EGPA from common conditions such as asthma and other differential diagnoses such as hypereosinophilic syndrome, infection or malignancies. In line with other multisystem inflammatory conditions, patients are commonly referred to and managed by rheumatology teams in the longer term, but may also be under renal, respiratory, cardiology, neurology, dermatology, haematology and ENT teams as required. Specialist Rheumatology and Renal MDTs are now required for discussion and management of biologics in the case of other types of ANCA associated vasculitis, connective tissues diseases and large vessel vasculitides, and this is where complex EGPA patients are also often discussed and managed within local networks. Patients with refractory or relapsing EGPA and asthma symptoms are then referred to acute severe asthma services hosted within respiratory departments to assess for anti-IL5 therapy eligibility. Patients would then be followed up jointly between respiratory and rheumatology for example. In some cases, patients are referred from Respiratory teams to Rheumatology if their clinical picture evolves from that of severe asthma to EGPA vasculitis. Then management would also be shared between specialities. However, this inevitably can lead to delays in initiating appropriate treatment. We know that access to specialist vasculitis MDT care is associated with better outcomes (e.g https://pubmed.ncbi.nlm.nih.gov/38782514/) but we appreciate that services are not well developed in all regions. In some cases patients can be followed up in individual specialities without referral to an MDT which is not ideal. The upcoming 2025 BSR management guidelines for ANCA vasculitis will highlight the importance of access to specialist multidisciplinary MDTs, as they have been shown to improve patient outcomes including reducing the number of serious infections and emergency admissions to hospital (VOICES study- Hollick Lancet Rheum 2024).
9c. What impact would the technology have on the current pathway of care?	In terms of access to benralizumab for EGPA, rather than just severe asthma, we would anticipate that patients could be assessed and treated within the context of established specialist MDTs for connective tissue disease and vasculitis within rheumatology and renal departments. These MDTs already incorporate appropriate multidisciplinary expertise, and biological nursing and pharmacy support for other diseases - so this would just be an additional indication and treatment to add to this. Complex EGPA patients are already discussed within

	these MDTs, for example if patients have severe or refractory disease and need consideration of cyclophosphamide or Rituximab, or referral to the severe asthma team, so this technology would not unduly impact on MDT capacity within rheumatology or renal departments. Although MDT provision is not uniform across the country, the introduction of Avacopan for AAV for example (which requires MDT discussion to complete the Blueteq) has promoted the development of new MDTs within renal departments, including regional networks to open access to smaller trusts. Rheumatology specialist centre MDTs are already used for the discussion of complex cases and biologics since the advent of Rituximab for AAV, myositis and lupus and Belimumab for lupus, so it was relatively straightforward to incorporate Avacopan into this setting. Overall, the use of this TA for people with relapsing or refractory disease may reduce the number of flares of disease people with EGPA have, and thereby reduce pressure on rheumatology, renal and respiratory nursing helplines, plus free up acute flare slots in outpatient clinics and inpatient beds overall.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Patients with severe asthma as a manifestation of EGPA may already receive benralizumab via existing commissioned routes in specialist asthma services. Patients with asthma who do not meet severity criteria for biologic therapy, even if severe non-asthma manifestations of EGPA are present (e.g., cardiomyopathy, neuropathy, kidney disease etc) do not currently have access to treatment so this will change to allow greater equity of access to patients managed in rheumatology and renal departments regardless of exact disease phenotype of EGPA. We propose that Benralizumab for EGPA patients should be assessed, discussed and managed by established specialist rheumatology and renal MDTs that already have expertise in the multi-system nature of EGPA and the infrastructure and experience in the use of biologics in other forms of vasculitis and connective tissue disorders.
10a. How does healthcare resource use differ between the technology and current care?	We anticipate that fewer patients with EGPA should flare on this treatment, therefore reduction in pressure on primary care, and secondary care acute emergency services, nurse specialist helplines, and acute specialist outpatient and inpatient services. This is subcutaneous therapy and therefore should not impact on day case capacity for infusions. Potentially the availability of this medication may raise awareness across other specialities and improve overall care of multisystem disease by requiring discussion within an experienced MDT meeting setting.

	There may also be a reduction in healthcare resource required to manage long-term side effects of steroids (osteoporosis, hip fracture, diabetes, infection and cardiovascular disease).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (with specialist MDT oversight) and specialist clinics, including multi-disciplinary vasculitis clinics, i.e., established NHS England rheumatology and renal specialist MDTs.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Therapy can be delivered and self-administered at home using existing specialist nurse and pharmacy pathways. There must be investment in ensuring timely delivery to ensure prompt start to medication in acute presentations, specifically ensuring hospital pharmacists have supply available to get a patient started as it can take 4-6 weeks to get home delivery established. Some additional training (nursing, pharmacy, patients) may be required as the treatment is introduced to clinical practice, but biologic nurses within rheumatology and renal teams will be experienced in similar biological medications in terms of administration, counselling and monitoring.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – RCT and observational studies demonstrate significant reduction in the number of flares of EGPA, cumulative glucocorticoid burden and adverse effects and higher rates of glucocorticoid free remission.
11a. Do you expect the technology to increase length of life more than current care?	Yes. The five factor score highlights key items predictive of mortality of EGPA including renal involvement, proteinuria, cardiomyopathy, gastroenterology involvement and neurological involvement. These disease manifestations would not qualify a patient for anti IL5 treatment at present under the acute severe asthma pathway. Reducing this inequality may help mortality and morbidity directly via access to effective treatment of active refractory disease in EGPA. Reducing flares should also reduce total cumulative glucocorticoid burden and avoid the use of high dose glucocorticoids in severe disease- this may reduce mortality from steroid side effects including severe infections, osteoporosis and fracture, diabetes and cardiovascular disease.

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. As our patients tell us, in the current situation, the impact of active relapsing disease and adverse effects of high dose glucocorticoids to treat flares, can have a significant impact on health related quality of life in people with EGPA “...in my personal life. Probably in my work life...I would find myself going into extremely dark holes. I'd start an argument, and go down an argument that I knew that was complete stupid argument, but couldn't back off of it, and then have to go... So all that was all part of, of, of when I got these flare-ups, and then the constant treatment of steroids (51-year-old male, EGPA, UK)”. Unrelated to asthma manifestations, patients with EGPA experience high symptom burden due to multisystem nature of disease – chronic rhinosinusitis, debilitating neuropathy, and symptoms related to cardiac failure are particularly challenging. Access to a proven therapy that increases periods of disease-free remission will have a significant and long-term impact on quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	RCT evidence supports use of benralizumab in relapsing or refractory glucocorticoid-dependent EGPA. We would support use in EGPA in patients within induction phase if they have refractory disease to other medications, in line with other biologics used in CTD and vasculitis, and also in relapsing disease.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Therapy is administered subcutaneous auto-injector, acceptable to nearly all patients. Observational data suggests treatment with benralizumab permits withdrawal of oral immunosuppressants in a significant proportion (>25%) of patients. There is also no specific blood monitoring required for Benralizumab, in comparison with conventional DMARDS and cyclophosphamide.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Adverse effects to medications in line with SPC. Stop rules should be decided by consensus with experts within EGPA but potential stop rules to consider could be: No overall reduction in number of flares (of note may be unrealistic to achieve zero flares in this disease so potentially a percentage reduction or consideration of minor versus major flares) Inability to reduce glucocorticoid dose over period of time (of note may not reach zero prednisolone so potentially a percentage reduction) Potentially should consider progress over 2 year course however rather than 3 or 6 months, due to episodic nature of disease flares, and worsening during winter. This would be in line with use of Rituximab maintenance in ANCA associated vasculitis whereby a two year course is prescribed and people are only stopped if they have adverse effects.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No – should impact on quality of life and potentially also quantity of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Yes, the technology is innovative – potentially the first targeted anti-cytokine therapy to be recommended for treatment of EGPA in the UK, with RCT and high-quality observational data to support its use. The only other therapy supported by RCT evidence in EGPA is cyclophosphamide, which is usually reserved for life- or organ-threatening disease and associated with significant toxicity.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes, this would represent a step change in management of EGPA. Firstly through use of first targeted biologic therapy for EGPA that has RCT evidence and national and international recommendation support. Secondly, by bringing anti-IL5 use within remit of rheumatology and renal specialist MDTs, this should support greater MDT multidisciplinary working and thereby improve patient care and outcomes in general. This should support greater equity of access to this targeted and well tolerated therapy for all patients with EGPA, regardless of disease manifestation.
16b. Does the use of the technology address any particular unmet need of the patient population?	Evidence indicates that benralizumab treatment extends periods of disease-free remission and permits glucocorticoid reduction and withdrawal, clear areas of unmet need in management of this disease.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	We are not aware of any long-term safety issues in patients already treated for severe asthma with this therapy for extended periods and the treatment has been tolerated within trials in EGPA.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In the MANDARA study, the comparator treatment to Benralizumab was Mepolizumab; Mepolizumab is not commissioned for EGPA in the UK but was demonstrated to be effective in the MIRRA study.
18a. If not, how could the results be extrapolated to the UK setting?	Placebo-treated patients in the MIRRA study more likely to represent the current UK population treated with standard care in EGPA.
18b. What, in your view, are the most important	Sustained disease remission, glucocorticoid-minimisation, and quality of life – addressed in RCT and observational data. Survival – not primarily addressed in relatively short-term trial follow up.

Professional organisation submission

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis

14 of 18

outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Evidence in other, comparable, autoimmune rheumatic diseases shows that glucocorticoid dose and duration associates with development of cardiovascular disease and with mortality. Whilst specific data are lacking (largely due to disease rarity), we would expect this to hold in EGPA, and that reduction in glucocorticoid use would associate with reduced cardiovascular risk and improved survival in this patient group.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Published observational and 'real-world' data replicate RCT findings – with greater time spend in remission, reductions in glucocorticoid dose, increased glucocorticoid withdrawal, and ability to withdraw other immunosuppressive agents.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to Specialist Care: patients in underserved or rural areas may lack access to specialist services, which could limit equitable access to new therapies like benralizumab. However, with the drive to MDT working for all systemic vasculitides and connective tissues disorders, for agreement of high cost drugs, the addition of benralizumab may add to the hub and spoke networks developed within Rheumatology and Renal teams. Socioeconomic Disparities: self-administration of benralizumab at home may require additional patient education and training. Factors such as education level, healthcare literacy, housing stability, and access to healthcare resources could affect patients' ability to manage the treatment effectively. This is in common with other biological subcut medications given within rheumatology units; teams should continue to take this into account on a case by case basis, with additional resources for vulnerable patients. Cultural and Language Barriers: For patients from non-English-speaking or diverse cultural backgrounds, effective communication about disease management, self-administration, and potential side effects may require tailored support. The introduction of benralizumab may highlight the need for clearer, standardized pathways to ensure all eligible patients - regardless of location, clinician expertise, or health system constraints - can access this treatment.
21b. Consider whether these issues are different from issues with current care and why.	No, these issues are in common with other subcutaneous medications used within EGPA and other rheumatic conditions- for example methotrexate, and these issues can also be the case for oral medications that are in current use – for example methotrexate, glucocorticoids, azathioprine and mycophenolate.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• EGPA is a rare disease, and patients face significant unmet needs, including diagnostic delays, cumulative burden of glucocorticoids (with significant adverse effects and impact on health related quality of life) and a lack of other proven or licensed therapies, making effective alternatives like benralizumab highly desirable. • Approval of Benralizumab would align with best practice in the management of EGPA and is supported by recent guidance from EULAR, ACR and the upcoming BSR management guidelines. • Approval of Benralizumab for EGPA will improve equity of access for this treatment, via inclusion of a broader range of disease manifestations of EGPA (neuro, derm, cardiac, renal, haematological involvement) beyond severe asthma alone, and inclusion of a greater range of specialist MDTs (rheumatology, renal and vasculitis) to support their use. • Benralizumab is targeted therapy for use in EGPA, it is well tolerated with minimal side effects and no blood monitoring requirements, comparing favourably with the current alternatives of non-specific DMARDS and cyclophosphamide. • Benralizumab requires subcutaneous administration supporting use at home by patients, thereby reducing impact on infusion day units. Effective treatment of EGPA should also reduce impact on acute emergency services including A+E, inpatient and acute outpatient services currently required to treat active disease and glucocorticoid adverse effects.

Thank you for your time.

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Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Clinical expert statement

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In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 15th April**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Part 1: Treating relapsing or refractory eosinophilic granulomatosis with polyangiitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	██████████
2. Name of organisation	Cambridge University NHS Foundation Trust
3. Job title or position	████████████████████
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with eosinophilic granulomatosis with polyangiitis (EGPA)? ☒ A specialist in the clinical evidence base for EGPA or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for relapsing or refractory EGPA?	Disease remission with low dose or no glucocorticoid

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Disease remission with a daily prednisolone dose below 5mg/day and no relapse
10. In your view, is there an unmet need for patients and healthcare professionals in relapsing or refractory EGPA?	Yes, the majority of EGPA patients pursue a relapsing/refractory course
11. How is relapsing or refractory EGPA currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Primarily with unacceptably high doses of glucocorticoids often in combination with oral immune suppressives and biologic drugs (anti-IL5 such as mepolizumab or benralizumab) or rituximab Although recommendations statements are clear, many patients do not receive the current 'standard of care' due to poor organisation of clinical services for EGPA patients in the NHS. We follow the EULAR 2022 recommendations (Helmich et al, Annals of Rheumatic Disease 2023) Anti-IL5 therapies have been an important advance in the care of EGPA patients but no pathways for EGPA patients exist and access is restricted via severe asthma pathways which are not suitable and dose therapies too low. Development of NICE guidance for use of these therapies in EGPA would increase patient access, reduce variability in care and improve outcomes
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, we currently have limited access, as discussed above and then only to lower dose, less effective regimens.

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

- How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Anti-IL5 therapies could be used directly by physicians with primary responsibility for an EGPA patient. Anti-IL5 therapies would be used at the correct dose, i.e. the dose used in double blind placebo controlled trials in EGPA. The drugs have no significant cost in delivery or monitoring over and above routine care, the cost is in the drugs themselves.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Ye, very much so. We have been wanting direct access to anti-IL5 therapies for many years and were disappointed when NICE chose not to review mepolizumab for EGPA in 2017. This has held back the effective use of these agents. I also expect access to anti-IL5 to improve the organisation of care for patients within the NHS in an analogous way to the impact of anti-TNFs on rheumatoid arthritis in the late 1990s. Yes, the reduction in glucocorticoids and improved control of disease activity will directly improve quality of life for patients
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no subgroup within EGPA that we know anti-IL5 will be less effective. There are subgroups not studied for which we lack evidence though.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	It will be easier to use and will simplify care by reducing complications relating to steroid medication.

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Additional testing will not be required. Rules to start should align with the eligibility criteria of the registration studies. We do not know when to stop but futility rules could be designed. In current practice we are continuing anti-IL5 long term in the majority of patients and the extension data from MIRRA and MANDARA is validating this approach.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, conventional QALY calculation underestimate the long term harm of glucocorticoids.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes, anti-IL5 is innovative, effective and has led to a step change in therapy. Yes, anti-IL5 partially addresses concern over our inability to achieve stable remission at a reasonable steroid dose.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	We have quite extensive experience over more than 10 years now and have collaborated with larger European surveys and are

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

	satisfied with the overall safety and acceptability of anti-IL5 therapies.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	They directly address the larger part of EGPA practice but do not address the new onset patient with major organ disease because this subgroup was excluded from the trials. Surrogate outcomes were not used. One or two rare adverse events have occurred that were not seen in the EGPA trials but have been seen in the wider severe asthma experience.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes, the larger European observational cohorts, where success was largely in line with the trials. Eg: Mattioli et al J Autoimmunity 2025
22. How do data on real-world experience compare with the trial data?	Very similar, we have over 60 patients currently on anti-IL5
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	There are no equality issues, apart from the problem of EGPA being a rare disease that has had little research and a small evidence base from which to make recommendations.

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Anti-IL5 therapies are already part of the standard of care of EGPA patients

A positive NICE recommendation will improve access to these therapies and will drive up the quality of care of EGPA patients

Glucocorticoids are toxic and the EGPA population tends to require high and prolonged dosing

Efficacy of anti-IL5 is consistent across clinical trials and observational experience

Anti-IL5 therapies are safe

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Clinical expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) or caring for a patient with it. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm on 21st April**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Part 1: Living with this condition or caring for a patient with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA)

Table 1 About you, relapsing or refractory EGPA, current treatments and equality

1. Your name	[REDACTED]
2. Are you (please tick all that apply)	☒ A patient with EGPA? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with EGPA? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Vasculitis Uk
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with EGPA? If you are a carer (for someone with EGPA) please share your experience of caring for them	My experience and symptoms included Lung pain, coughing, fatigue, weakness, joint pain, numbness, pins and needles, night sweats, trouble sleeping, head aches, breathlessness, sinus issues, rashes. My mobility was severely affected which effected my work routine
7a. What do you think of the current treatments and care available for relapsing or refractory EGPA on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Initial treatment high dose steroids (prednisolone). The side effects were bad and affected both home and work, these included.woolly, memory issues, mania, bad tempered, difficulty sleeping and weight gain. First steroid sparing drug was mycophenolate (3g per day) – I experienced 24/7 chest pain managed to taper pred to 15-25 during a 3 month period. Azathioprine (150mg/day). I experienced 24/7 nausea, dizziness, vomiting. Mepo tapered pred to 7.5 some pain and woolliness some symptoms started to return on reduction below 7.5. Moving to benralizumab has been life changing both home and work life are back to normal. I have some fatigue but this is manageable. I have managed to completely taper off Pred!

Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

8. If there are disadvantages for patients of current NHS treatments for relapsing or refractory EGPA (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Side effects of pred as above. Myco and Aza very bad for me. Both gave 24/7 pain. No adverse effects with Benra to date (2 years plus) and off pred.
9a. If there are advantages of benralizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does benralizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	A. With Benra life changing. Near normal work and home life and tapering completely off pred a big bonus of all. I can focus at work and travel to the office. My memory is better. B. Normal home and work life. My wife and work colleagues are seeing a person they recognise. C. No known side effects from benra to date. Plenty of nasty and potentially serious side effects from pred, myco and aza as previously described.
10. If there are disadvantages of benralizumab over current treatments on the NHS please describe these. For example, are there any risks with benralizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No disadvantages that I have experience to date with Benra.
11. Are there any groups of patients who might benefit more from benralizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Benra managing my egpa, whilst we are a small group I am sure others would benefit. I have a small egpa whatsapp group and without a doubt the 3 of us on Benra have less problems.

Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

12. Are there any potential equality issues that should be taken into account when considering relapsing or refractory EGPA and benralizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No
13. Are there any other issues that you would like the committee to consider?	Seems I am more fortunate than others with egpa both from an early diagnosis and access to benra

Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Benra has allowed me to have a near normal life at home and at work
- I have tapered completely off pred and its nasty side effects
- I understand Benra targets only eosinophils and allows me to have part of an immune system. I believe all other treatments adversely effect the immune system
- I have more confidence in mobility, travel and self determination
- My wife has confidence in my ability to lead a normal life and I am less of a burden

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Patient expert statement

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]



Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

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Date completed	14 th February 2025

Source of funding:	This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR136182.
Declared competing interests of the authors:	During the course of the project Nick Meader accepted a role with GSK which are a comparator company. None of the other authors or the clinical advisors to the EAG have any competing interests to declare.
Contributions of authors:	Julia Whitehall and Katie Thomson assessed the effectiveness evidence and wrote the first draft of the effectiveness section with support from Ayomikun Ogunyemi. Sheila Wallace and Madeleine Still assessed the searches and wrote the sections relating to these. Nick Meader provided advice on the ITC and the MAIC. Gill Norman edited and commented on all aspects of the effectiveness appraisal. Stephen Rice acted as project lead and lead health economist. Najmeh Moradi and Lakshmi Jayachandran assessed the health economics evidence.
Acknowledgements:	The authors are grateful to the following clinical experts for their advice to the EAG: Jonathan Heaney and Wezi Sendama.
Rider on responsibility for the report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows:	Whitehall J, Moradi N, Jayachandran L, Thomson K, Ogunyemi A, Wallace S, Still M, Meader N, Norman G, Rice S. Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]: A single technology appraisal. Factual accuracy check (FAC) response version. Newcastle upon Tyne, UK: Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University; 2025.
Report key:	Commercial in confidence (CiC) data are highlighted in blue throughout the report. Any de-personalised data are highlighted in pink throughout the report.

Abbreviations

AAV	ANCA-associated vasculitis
ACQ-6	Asthma control questionnaire (6-item version)
AE	Adverse events
ANCA	Anti-neutrophil cytoplasmic antibody
ARR	Annualised relapse rate
BMI	Body mass index
BNF	British national formulary
BVAS	Birmingham Vasculitis Activity Score
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CNS	Central nervous system
CPRD	Clinical Practice Research Datalink
CS	Company's submission
CSR	Clinical study report
CYC	Cyclophosphamide
DB	Double blind
DSA	Deterministic sensitivity analysis
DSP	Disease specific programme
DSU	Decision Support Unit
EAACI	European Academy of Allergy and Clinical Immunology
EAG	Evidence Assessment Group
ECG	Electrocardiogram
eCVD	Established cardiovascular disease
EE	Economic evaluation
ED	Emergency department
EGPA	Eosinophilic granulomatosis with polyangiitis
EMC	Electronic medicines compendium
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	The 5-level EQ-5D version
ERS	European Respiratory Society
EULAR	European League Against Rheumatism
FAS	Full set analysis
FDA	Food and Drug Administration
FFS	Five-factor score
GP	General practitioner
GPA	Granulomatosis with polyangiitis
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IS	Immunosuppressant
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

ITC	Indirect treatment comparison
ITT	Intention-to-treat
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MPA	Microscopic polyarteritis
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NHSEED	NHS Economic Evaluation Database
NI	Non-inferiority
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
OCS	Oral corticosteroid
OLE	Open- label extension
OMERACT	Outcome Measures in Rheumatology
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PAV	Probabilistic analysis values
PCS	Physical component summary
PfC	Points for clarification
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
Q4W	Every 4 weeks
RePEc	Research papers in Economics
RCT	Randomised controlled trial
RR	Rate ratio
RTX	Rituximab
SAE	Serious adverse events
SC	Subcutaneous
SE	Standard error
SF-36V2	Short form 36-item health survey (version2, acute recall)
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SLR	Systematic literature review
SNOT-22	Sino-nasal outcome test-22
SoC	Standard of care
SSQ	Sino-nasal symptoms questionnaire
STA	Single Technology Appraisal
TAR	Technology Assessment Reviews
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse events
TTO	Time trade-off

TTOT	Time-to-off treatment
UK	United Kingdom
USA	United States of America
VDI	Vasculitis damage index
wk	Week
WPAI	Work productivity and activity impairment questionnaire

Table of Contents

Source of funding:	2
1 EXECUTIVE SUMMARY	12
1.1 Overview of the EAG's key issues	12
1.2 Overview of key model outcomes	12
1.3 Description of the EAG's key clinical and economic issues	14
1.4 Summary of the EAG's preferred assumptions and ICER	20
2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM	24
2.1 Population	32
2.2 Comparators	34
2.3 Outcomes	35
2.4 Special considerations including issues related to equality	40
3 CLINICAL EFFECTIVENESS	42
3.1 Critique of the methods of review(s)	42
3.1.1 Search methods for the clinical effectiveness SLR	43
3.1.2 Search strategies	43
3.1.3 Eligibility criteria	44
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)	47
3.2.1 MANDARA	47
3.2.2 MIRRA trial	56
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison	67
3.3.1 Bucher ITC	67
3.3.2 Matching-adjusted indirect comparison	73
3.4 Conclusions of the clinical effectiveness section	75
4 COST EFFECTIVENESS	77
4.1 EAG comment on company's review of cost effectiveness evidence	77
4.1.1 Search methods for the cost effectiveness review	78
Search strategies	78
4.1.2 Conclusions of the cost effectiveness review	78
4.2 Summary and critique of company's submitted economic evaluation by the EAG	78
NICE reference case checklist	78
4.2.1 Model design and assumptions	82
4.2.2 Model structure/design	86
4.2.3 Baseline transition probabilities and proportion of patients in refractory sub-state	90
4.2.4 Treatment effectiveness	95
4.2.5 Adverse events	96
4.2.6 Health-related quality of life	96
4.2.7 Resources and costs	101
5 COST EFFECTIVENESS RESULTS	107
5.1 Company's cost effectiveness results based on original model	107

5.2	Company's sensitivity analyses	108
5.2.1	Deterministic sensitivity analysis	108
5.2.2	Probabilistic sensitivity analysis	110
5.2.3	Scenario analysis.....	113
5.3	Company's cost effectiveness results based on the updated model	115
5.3.1	Company's cost effectiveness results based on the updated model.....	115
5.4	Company's sensitivity analyses based on the updated model.....	117
5.4.1	Deterministic sensitivity analysis	117
5.4.2	Probabilistic sensitivity analysis	117
5.5	Model validation and face validity check	122
5.5.1	Face validity assessment and technical verification	122
5.5.2	Comparison with external data.....	122
6	EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES	126
6.1	Exploratory and sensitivity analyses undertaken by the EAG.....	126
6.1.1	EAG Base-case	126
6.1.2	EAG exploratory scenario analyses	127
6.1.3	EAG subgroup analyses	137
6.2	Impact on the ICER of additional clinical and economic analyses undertaken by the EAG.....	138
6.2.1	The EAG base case results	138
6.2.2	EAG Deterministic Sensitivity Analysis.....	140
6.2.3	EAG Probabilistic Sensitivity Analysis	140
6.2.4	Company deterministic scenario analyses on the EAG base case	143
6.2.5	EAG Exploratory Scenario Analysis	146
6.3	Overall conclusions of the EAG's cost-effectiveness analysis.....	149
6.4	Overall conclusions of the EAG's critique	149
7	References.....	152
8	Appendices.....	158
8.1	A.1 Survival model.....	158
8.2	A.2 Scenario 6	162
8.3	A.3 Scenario 7	163
8.4	A.4 SoC with OCS versus SoC without OCS efficacy	164

Table of Tables

Table 1.1: Summary of EAG's key issues	12
Table 1.2: Key issue 1: Company's trial results may not be generalisable to all EGPA patients (i.e. those with severe EGPA)	14
Table 1.3: Key issue 2: EGPA state utility estimates	14
Table 1.4: Key issue 3: benralizumab discontinuation rate	15
Table 1.5: Key issue [4] The relationship between benralizumab discontinuation and OCS discontinuation	17
Table 1.6: Key issue [5] OCS discontinuation rate	18
Table 1.6: Key issue [6] No treatment waning	19
Table 1.7: Probabilistic results from company base-case and EAG base-case	20
Table 1.8: Selected results from company after clarification and EAG's deterministic scenario analysis	22
Table 2.1: Statement of the decision problem (as presented by the company)	24
Table 2.2: Annual asthma exacerbation rate ratio at 56 weeks showing subgroup analysis by exacerbations in the previous year (data from the CALIMA trial for patients with severe, uncontrolled, eosinophilic asthma).	33
Table 2.3: Summary of outcome data in the MANDARA and MIRRA trials and in the indirect treatment comparisons	36
Table 3.1: Summary of the EAG's critique of the systematic literature review	42
Table 3.2: Eligibility criteria for the identification of studies to be included in the SLR	45
Table 3.3: Summary of EAG's critique on the design, conduct and analysis of the MANDARA trial	47
Table 3.4: OCS dosage and proportion of IS use by country, UK site, and overall study population from the MANDARA trial	55
Table 3.5: Summary of EAG's critique on the design, conduct and analysis of the MIRRA trial	61
Table 3.6: Accrued duration of remission over 52-week treatment period according to subgroup	66
Table 3.7: Summary of EAG's critique of the Bucher ITC methods	67
Table 3.8: Bucher ITC and MAIC results	72
Table 3.9: Summary of the EAG's critique of the MAIC methods	73
Table 3.10: Ranking of Potential Treatment Effect Modifiers	74
Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness	77
Table 4.2 : NICE reference case checklist	79
Table 4.3: Summary of EAG's critique on the design of the economic model	82

Table 4.6: Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort	94
Table 4.4: Mortality inputs	94
Table 4.7: Summarises the EAG's critique on HRQoL within the economic model.....	96
Table 4.8: Patients with organ damage in the Adelphi DSP Study	99
Table 4.9: Breakdown of patients with organ damage in Adelphi DSP Study	99
Table 4.10: Health state utility values	100
Table 4.11: Disutility values in the OCS sub-model	100
Table 4.12: Summary of EAG's critique on resources and costs within the economic model	101
Table 4.13: Treatment Acquisition Costs.....	105
Table 4.14: Frequency of healthcare resource use, by health state, per patient per year for disease management.....	106
Table 4.15: Unit Costs for Disease Management	106
Table 5.1: Company base-case cost-effectiveness results	107
Table 5.2: Company base-case results for net health benefit.....	107
Table 5.3: Company base-case results for net monetary benefit.....	107
Table 5.4: Company's deterministic sensitivity analysis.....	108
Table 5.5: Company's probabilistic sensitivity analysis.....	110
Table 5.6: Company's probabilistic sensitivity analysis results for net health benefit	110
Table 5.7: Company's probabilistic sensitivity analysis results for net monetary benefit	110
Table 5.8: Probabilistic scenario analysis results for the company base-case	113
Table 5.9: Company base-case cost-effectiveness results (updated model)	115
Table 5.10: Company base-case results for net health benefit (updated model)	115
Table 5.11: Company base-case results for net monetary benefit (updated model)	115
Table 5.12: Breakdown of cost in company base-case result (updated model)	116
Table 5.13: Breakdown of QALY in company base-case result	116
Table 5.14: Company's probabilistic sensitivity analysis	117
Table 5.15: Company's probabilistic sensitivity analysis results for net health benefit (updated model).....	118
Table 5.16: Company's probabilistic sensitivity analysis results for net monetary benefit (updated model).....	118
Table 5.17 Deterministic scenario analysis results for the company base-case (updated model).....	120
Table 6.1: Morality hazard ratios vs EGPA/no event	127

Table 6.2: Hazard ratios versus the general population.....	128
Table 6.3 Proportion of patients in EGPA health states while receiving SoC in the benralizumab arm at different time points.....	132
Table 6.4 Transition probabilities for SoC after discontinuation of benralizumab	133
Table 6.5: Deterministic/probabilistic EAG base-case	138
Table 6.6: EAG Base-case Result for Net Health Benefits	139
Table 6.7: EAG Base-case Result for Net Monetary Benefit.....	139
Table 6.8: EAG Deterministic Sensitivity Analysis	140
Table 6.9: EAG base-case probabilistic sensitivity analysis result.....	141
Table 6.10: Company deterministic scenario analyses on EAG base-case	144
Table 6.11 EAG deterministic scenario analyses	146
Table A.1: Morality hazard ratios vs EGPA/no event	158
Table A.2: Hazard ratios versus the general population	158

Table of Figures

Figure 2.1: Proposed positioning of benralizumab for patients with EGPA	32
Figure 3.1: OCS usage by country across the 52-week trial period (full MANDARA population)	56
Figure 4.1 Cost-effectiveness model	87
Figure 4.2 OCS-sub model structure	88
Figure 4.3 Classification of patients in disease states from CPRD	91
Figure 4.4 Model structure parameterisation by benralizumab arm	92
Figure 4.5 Model structure parameterisation by SoC arm	93
Figure 4.6: OCS usage by country across the 52-week trial period (full MANDARA population)	104
Figure 5.1: DSA tornado diagram for ICER for benralizumab versus SoC (with PAS)	109
Figure 5.2 ICER convergence plot for benralizumab versus SoC (with PAS)	111
Figure 5.3 Probabilistic cost-effectiveness plane for benralizumab versus SoC (with PAS).....	111
Figure 5.4 Cost-effectiveness acceptability curve for benralizumab versus SoC (with PAS)	112
Figure 5.5: DSA tornado diagram for ICER for benralizumab versus SoC with PAS (updated model).....	117
Figure 5.6: Probabilistic cost-effectiveness plane for benralizumab versus SoC with PAS (updated model).....	119

Figure 5.7: Cost-effectiveness acceptability curve for benralizumab versus SoC with PAS (updated model).....	119
Figure 5.8 Model prediction of survival by treatment arm	122
Figure 5.9: Model prediction of OCS-related chronic events, benralizumab arm	123
Figure 5.10: Model prediction of OCS-related chronic events, SoC arm.....	123
Figure 5.11: Model prediction of OCS-related acute events, benralizumab arm	124
Figure 5.12: Model prediction of OCS-related acute events, SoC arm	124
Figure 5.13: Model prediction of health state occupancy; benralizumab arm.....	125
Figure 5.14: Model prediction of health state occupancy; SoC arm	125
Figure 6.1 The proportion of patients alive over time for benralizumab and SoC (Scenario 1)	129
Figure 6.2 The proportion of patients alive over time for benralizumab and SoC (Scenario 2)	130
Figure 6.3: The proportion of patients receiving SoC who receive OCS (after benralizumab discontinuation).....	134
Figure 6.4: The model prediction for the number of patients receiving benralizumab	135
Figure 6.5: DSA tornado diagram for ICER for benralizumab versus SoC.....	141
Figure 6.6: EAG base-case Cost-effectiveness Plane	142
Figure 6.7: EAG base-case Cost-effectiveness Acceptability Curve.....	142

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 identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 2 to 6).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	Company's trial and ITC results may not be generalisable to all EGPA patients (i.e. those with severe EGPA).	3.1, 3.2, 3.3
2	EGPA state utility estimates: the utility estimates of the refractory and relapse states may be underestimates.	4.2.5, 4.2.6
3	Discontinuation rate of benralizumab: there was uncertainty in the evidence for a ■ discontinuation rate for benralizumab.	4.2.2.3, 4.2.2.4
4	The relationship between benralizumab discontinuation and OCS discontinuation: assumptions around benralizumab discontinuation if a patient discontinues OCS and OCS use if a patient discontinues benralizumab may not be realistic.	4.2.2.3, 4.2.2.4
5	OCS discontinuation rate: the OCS discontinuation rate was assumed to be constant at ■ per year. This may be unrealistic.	4.2.2.3, 4.2.2.4
6	No treatment waning effect. Any change to this assumption would significantly increase the ICER for benralizumab.	4.2.1
Abbreviations: EAG= Evidence Assessment Group, EGPA= eosinophilic granulomatosis with polyangiitis; DB= double blinded; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OCS = oral corticosteroid; RCT= randomised controlled trial;		

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:

- Response rate: Increase the proportion of patients who achieve remission. This affects QALYs in three ways: (1) through the higher utility associated with the remission state, (2) the lower OCS dose, which results in lower disutility associated with OCS-associated acute and chronic adverse events, and (3) through a lower SMR than the stable disease or relapse health states.
- Annualised Relapse rate: Decrease the proportion of patients in the relapse state. This affects QALYs in two ways: (1) through the lower utility associated with the relapse state, (2) the higher OCS dose associated with the relapse state, which affects the disutility associated with OCS-associated acute and chronic adverse events.
- Reduce the proportion of patients in the refractory state within the stable state: the refractory state has the lowest estimated utility value because the patient experienced severe depression, anxiety and other symptoms that significantly affected the quality of life of patients.
- Reduce the percentage of patients receiving OCS. This affects the disutility associated with OCS-associated acute and chronic adverse events by reducing the cumulative OCS dose overall.

Overall, the technology is modelled to affect costs by:

- Proportion of patients on benralizumab: With PAS price applied to benralizumab and not for the standard of care, benralizumab is still the treatment with highest acquisition cost among EGPA treatments.
- Response rate: Increase the proportion of patients who achieve remission. This affects costs in two ways: (1) through the lower costs associated with the remission state, (2) the lower OCS dose, which results in lower cost associated with OCS-associated acute and chronic adverse events.
- Annualised Relapse rate: Decrease the proportion of patients in the relapse state. This affects costs in two ways: (1) through the higher cost associated with the relapse state, (2) the higher OCS dose associated with the relapse state, which affects the cost associated with OCS-associated acute and chronic adverse events.
- Reduce the percentage of patients receiving OCS. This affects the cost associated with OCS-associated acute and chronic adverse events by reducing the cumulative OCS dose overall.

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

- The no treatment waning assumption has the greatest effect. The drivers of the model are the effect of benralizumab on the numbers of patients in remission and in the non-refractory state.
- The implicit related modelling assumptions that patients who discontinue OCS and those who do not are equally likely to discontinue benralizumab, and if patients discontinue OCS then they do not restart OCS if they discontinue benralizumab.
- Related to the previous, the assumption that the effectiveness of SoC with OCS treatment is the same as SoC without OCS treatment.
- The benralizumab discontinuation rate remains constant for the duration of the model.

1.3 Description of the EAG's key clinical and economic issues

Table 1.2: Key issue 1: Company's trial results may not be generalisable to all EGPA patients (i.e. those with severe EGPA)

Report section	3.1, 3.2, 3.4
Description of issue and why the EAG has identified it as important	The clinical effectiveness evidence for benralizumab as an add-on treatment for patients with refractory or relapsing EGPA is derived from the MANDARA and MIRRA trials.^{1,2} Both trials use similar study designs, patient characteristics, and outcomes which, along with the inclusion of a common comparator, permit an ITC to compare additional benralizumab treatment to oral corticosteroids (OCS) with or without immunosuppressants (IS). However, both studies excluded patients presenting with organ- or life-threatening EGPA at the time of screening. Clinical advice to the EAG confirms benralizumab would be a relevant treatment option for this subpopulation of patients presenting with severe disease, who are more likely to receive treatment with agents including cyclophosphamide or rituximab. Cyclophosphamide and rituximab were also listed as prohibited medications in the MANDARA and MIRRA trials.^{1,2} There is therefore a lack of evidence on the efficacy and safety of benralizumab in patients with severe EGPA, who may also be receiving cyclophosphamide or rituximab. This means that there is also uncertainty about cost effectiveness modeling as it relates to this group.
What alternative approach has the EAG suggested?	The EAG has no suggested alternatives.
What is the expected effect on the cost effectiveness estimates?	Due to the uncertainties and lack of evidence for patients with severe EGPA, the EAG is unable to comment on what effect this would have on the cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	RCT evidence from the severe asthma population may provide additional supportive information. Additionally, if benralizumab receives a NICE recommendation, real-world evidence could be collected in UK clinical practice to help provide conclusions on the effectiveness and cost-effectiveness in patients with severe EGPA.
Abbreviations: EAG= Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; IS= immunosuppressant; ITC= indirect treatment comparison; OCS = oral corticosteroid; RCT = randomised controlled trial; IS= immunosuppressant; NICE= National Institute for Health and Care Excellence; UK= United Kingdom.	

Table 1.3: Key issue 2: EGPA state utility estimates

Report section	4.2.5, 4.2.6
Description of issue and why the EAG has identified it as important	To inform EGPA state utility values in the economic model, the company used utility estimates derived from the Adelphi DSP study. ³ ■ of the 177 participants suffered from various organ damage, which are severe adverse events, due to EGPA and the treatment received.

Report section	4.2.5, 4.2.6
	There was a significant risk of overlap for these with the OCS-associated adverse events. Disutilities for OCS-associated adverse events were included in the model separately, so ideally the EGPA state utility estimates should not include OCS-associated adverse event disutilities. If patients in the refractory and relapse states are more likely to experience OCS-associated adverse events, then the utilities in these are more likely to be underestimated than the non-refractory and remission states.
What alternative approach has the EAG suggested?	The EAG suggests scenario analyses where the utility estimates for the refractory and relapse states are adjusted for OCS-associated adverse event disutilities.
What is the expected effect on the cost effectiveness estimates?	Increasing the utility of refractory and relapse utility estimates relative to remission and non-refractory utility estimates will reduce the QALY benefit of benralizumab in increasing the number of patients in the remission and non-refractory states.
What additional evidence or analyses might help to resolve this key issue?	A form of regression analysis could be conducted using the 177 patients from the Adelphi DSP study with the OCS-associated adverse events included in this economic model as covariates alongside the 4 EGPA states. Where multicollinearity is present an adverse event may need to be removed and a description of the multicollinearity noted. The sample size is not very large for this analysis. Otherwise, providing a breakdown of percentage of participants across the EGPA disease states with OCS acute and chronic events could potentially provide information to help adjust the state utility estimates to remove OCS-related disutilities. Appropriate scenario analyses around EGPA state utility analyses can then be done. Finally, further data collection would provide the additional sample size required for accurate estimates, although the EAG recognizes the low prevalence of the disease.
Abbreviations: EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; Adelphi DSP = Disease Specific Programmes; ICER = incremental cost-effectiveness ratio; OCS = oral corticosteroids.	

Table 1.4: Key issue 3: benralizumab discontinuation rate

Report section	4.2.2.3, 4.2.2.4
Description of issue and why the EAG has identified it as important	The company assumed a discontinuation rate of ■ per year for benralizumab in the CS model.

Report section	4.2.2.3, 4.2.2.4
	The discontinuation rate observed in the MANDARA DB trial was [REDACTED]. But evidence from other sources informed the rate to be in the range of 8-12%. The discontinuation rate informed by MANDARA OLE was [REDACTED] and severe asthma patients on benralizumab was [REDACTED].^{4,5} Hence, there was a significant level of uncertainty in the treatment discontinuation rate for benralizumab.
What alternative approach has the EAG suggested?	The EAG has suggested exploratory scenario analyses using discontinuation rates informed by various sources – MANDARA DB ([REDACTED]), MANDARA OLE ([REDACTED]). The company conducted a scenario analysis with a [REDACTED] discontinuation rate.
What is the expected effect on the cost effectiveness estimates?	A lower discontinuation rate of [REDACTED] is expected to increase the ICER by around £2000/QALY. A higher discontinuation rate, say [REDACTED] is expected to decrease the ICER by around £2000/QALY.
What additional evidence or analyses might help to resolve this key issue?	Additional observational data on the use of benralizumab over time would help inform benralizumab discontinuation rates in EGPA.
Abbreviations: EAG = Evidence Assessment Group; ICER = Incremental Cost-effectiveness Ratio; QALY = Quality adjusted life years; CS = Company Submission; DB= double blind; OLE= open label extension.	

Table 1.5: Key issue [4] The relationship between benralizumab discontinuation and OCS discontinuation

Report section	4.2.2.3, 4.2.2.4
Description of issue and why the EAG has identified it as important	The following assumptions were not stated by the company but were implicit in the model: Assumption 1: The likelihood of response was the same for those who continued receiving OCS and those who discontinued OCS while on treatment. Responders continued receiving benralizumab. The likelihood of benralizumab discontinuation was the same for those who continued receiving OCS and those who discontinued OCS while on treatment. Assumption 2: Patients who discontinue OCS in the benralizumab arm do not restart OCS after discontinuing benralizumab. The consequence of these related assumptions is that the proportion of patients receiving SoC after benralizumab discontinuation who also receive OCS continually decreases over time. There is then the following implicit assumption in the CS model. Assumption 3: The effectiveness of SoC with OCS is the same as that for SoC without OCS. The transition probabilities for SoC are the same regardless of the proportion of patients receiving OCS. This last assumption contributes to a situation where the ICER for benralizumab lowers when the discontinuation rate for benralizumab increases. Essentially, SoC after benralizumab is associated with greater QALYs and lower costs than in the SoC arm of the model because of fewer OCS-associated acute and chronic events. The EAG acknowledges the limitation of evidence in this population, but the EAG is not convinced these assumptions appropriately reflect clinical practice. No evidence was provided to support any of them.
What alternative approach has the EAG suggested?	The EAG explored this uncertainty through different scenarios, where each of the assumptions in turn is removed from the model.
What is the expected effect on the cost effectiveness estimates?	Removing any one of the assumptions results in increased costs and lower QALYs for benralizumab and therefore a higher ICER.

Report section	4.2.2.3, 4.2.2.4
	The effect on the ICER of removing assumption (3) is very small unless OCS has a considerable effect on the likelihood of in being in better EGPA states. The effect of removing assumption (2) is small, increasing the ICER by £2,367. The effect of removing assumption (1) and alternatively assuming that the patients who discontinue OCS while on benralizumab never discontinue benralizumab has a greater effect on the ICER, increasing it by £7,723. This is because fewer patients discontinue benralizumab because of the assumption that those who discontinue OCS never discontinue benralizumab.
What additional evidence or analyses might help to resolve this key issue?	Given that ■ of patients in the MANDARA trial discontinued OCS during the first 12 months, the company could provide evidence on the likelihood of response for those who discontinued OCS and those who did not. Observational data may be required to provide evidence on the likelihood of discontinuing benralizumab having discontinued OCS. Observational data may be required to provide evidence on the likelihood of restarting OCS after benralizumab discontinuation if a patient discontinued OCS while on benralizumab. Clinical expert opinion could be sought on the plausibility of assumptions (1)-(3).
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; ICER = Incremental Cost-effectiveness Ratio; OCS = oral corticosteroid; QALY = Quality adjusted life years; SoC = standard of care	

Table 1.6:Key issue [5] OCS discontinuation rate

Report section	4.2.2.3, 4.2.2.4
Description of issue and why the EAG has identified it as important	The OCS discontinuation rate in the benralizumab arm was assumed to be ■% per year derived from MANDARA.⁵ It was assumed that this continued indefinitely. The EAG is not aware of any evidence to suggest that the OCS discontinuation rate would continue beyond 1 year at the same rate indefinitely. It seems plausible that the benefit of benralizumab would be achieved within a short period of time after the start of treatment.

Report section	4.2.2.3, 4.2.2.4
What alternative approach has the EAG suggested?	The EAG considers it quite possible that the OCS discontinuation rate will decline over time. In the EAG base case the discontinuation rate is assumed to decline linearly from ■% at year 1 to 0% at year 5. In a scenario analysis the OCS discontinuation rate was set to be 0% after 1 year.
What is the expected effect on the cost effectiveness estimates?	Modelling a linear decline in the OCS discontinuation rate from 1 year to 5 years barely changes the ICER. Setting the OCS discontinuation rate to 0% after 1 year increases the ICER by less than £1,000. The drivers of the model are the effect of benralizumab on the EGPA state transition probabilities and the reduction of the percentage of patients in the refractory state in the stable state. This issue has only been included as a key issue as it is anticipated that committee members might question the OCS discontinuation assumption.
What additional evidence or analyses might help to resolve this key issue?	Observational evidence of continuing benralizumab treatment would provide evidence on the discontinuation rate of OCS.
Abbreviations: EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; ICER = Incremental Cost-effectiveness Ratio; OCS = oral corticosteroids.	

Table 1.7: Key issue [6] No treatment waning

Report section	4.2.1
Description of issue and why the EAG has identified it as important	The company assumes that the effectiveness estimates for benralizumab at 12 months persist for the duration of treatments. Effectiveness estimates include: - The odds ratio of response (ITC estimate) - The annualized relapse rate (ITC estimate) - The reduction in percentage of stable patients who are refractory (MANDARA trial) No treatment waning was also assumed in TA565.⁶ Clinical expert opinion supported this. The EAG retained this assumption in the EAG analyses as it was felt that there was no basis to change it. But it is listed here as a Key Issue because these are the drivers of the model. Any change to the no treatment waning

Report section	4.2.1
	assumption will result in a significant increase in the ICER for benralizumab.
What alternative approach has the EAG suggested?	The EAG has not suggested an alternative. The EAG is highlighting to the committee that these effectiveness estimates drive the model results and therefore the no treatment waning assumption is critical.
What is the expected effect on the cost effectiveness estimates?	Any dilution to the no treatment waning assumption will result in a significant increase in the ICER for benralizumab.
What additional evidence or analyses might help to resolve this key issue?	Observational evidence against which the predicted percentage of patients in the EGPA states could be used to externally validate the model predictions for benralizumab.
Abbreviations: EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; ICER = Incremental Cost-effectiveness Ratio; ITC= indirect treatment comparison; OCS = oral corticosteroids.	

1.4 Summary of the EAG's preferred assumptions and ICER

Two changes were made from the company's base-case to the EAG base-case.

First, the EAG made utility adjustments in the health state utility values used to inform the model. The company obtained the utility values from the Adelphi DSP study³ while considering disutility values related to OCS use from the Gibson et al. (2024) study.⁷ The EAG made adjustments to avoid double counting the negative effects of OCS use, as the population in the Adelphi DSP study already suffered from adverse events which could overlap with OCS comorbidities.³

Second, the EAG modelled a linear decline in the OCS discontinuation rate from █% to 0% from 1 year to 5 years. The CS model assumed an annual rate of █% for the duration of benralizumab treatment.

The probabilistic results from the company and EAG base-case are shown in Table 1.8. Selected results from the company and EAG's deterministic scenario analysis are shown in Table 1.9.

Table 1.8: Probabilistic results from company base-case and EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Probabilistic (after clarification)					
Benralizumab + SoC	██████	████	██████	████	£27,166
SoC (OCS + IS)	██████	████	=	=	-
EAG base-case – Probabilistic					

Benralizumab + SoC	██████	██████	██████	██████	£32,174
SoC (OCS + IS)	██████	██████	=	=	-
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; IS= immunosuppressant; OCS= oral corticosteroids; SoC= standard of care.					

Table 1.9: Selected results from company after clarification and EAG's deterministic scenario analysis

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	██████	██████	£30,897
CS 4-1	Proportion of patients in refractory sub-state, within stable disease health state: Benralizumab arm: Starting % of █████%, then relative reduction applied (informed by MANDARA¹) to yield █████% at week 52) SoC arm: starting % of █████%, stayed constant (CPRD)⁸	Starting proportion of patients in refractory sub-state, within stable disease health state -5%	£██████	██████	£31,672
CS 4-2	Proportion of patients in refractory sub-state, within stable disease health state: Benralizumab arm: Starting % of █████%, then relative reduction applied (informed by MANDARA¹) to yield █████% at week 52) SoC arm: starting % of █████%, stayed constant (CPRD)⁸	Starting proportion of patients in refractory sub-state, within stable disease health state +5%	██████	██████	£29,990
CS 5-1	Adelphi DSP study ³	General population valuation from vignette study	██████	██████	£16,093

CS 5-2	Adelphi study ³	DSP	Patient valuation from vignette study	██████	████	£13,700
EAG 6	-		All of those who discontinue OCS do not discontinue benralizumab	██████	████	£33,388
EAG 10	-		Benralizumab discontinuation rate of █████	██████	████	£33,372
EAG 11	-		Benralizumab discontinuation rate of █████	██████	████	£28,743
EAG 12 (6 & 10)	-		Patients who discontinue OCS do not discontinue benralizumab and benralizumab discontinuation rate of █████	██████	████	£34,006
EAG 13 (6 & 11)	-		Patients who discontinue OCS do not discontinue benralizumab Benralizumab discontinuation rate of █████	██████	████	£33,157
EAG 5	-		Change to the Benralizumab_SoC transition probabilities C	██████	████	£33,165
EAG 7	-		Those who discontinue OCS restart OCS after discontinuing benralizumab	██████	████	£33,165
EAG 4	-		Change to the Benralizumab_SoC transition probabilities B	██████	████	£33,012

Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year; CPRD = Clinical Practice Research Datalink; Adelphi DSP = Adelphi Disease Specific Programmes; SoC = standard of care; OCS = oral corticosteroids

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy	In line with final scope	N/A	The population addressed excludes those characterised as having severe disease. This is justified based on the positioning of benralizumab in the treatment pathway but represents a key concern. Further details are provided in Section 2.1.
Intervention	Benralizumab	In line with final scope	Throughout the submission, benralizumab should be considered as benralizumab + SoC, where SoC is defined as OCS with or without stable IS. This aligns with the use of benralizumab in MANDARA ¹	Whilst the NICE scope states benralizumab, in the CS, the company states benralizumab should be considered with standard care (OCS with or without stable IS). The EAG is satisfied with this positioning.

Comparator(s)	Established clinical management without benralizumab, including: • OCS (do not currently have a marketing authorisation in the UK for this indication) • CYC (does not currently have a marketing authorisation in the UK for this indication) • Other IS agents (do not currently have a marketing authorisation in the UK for this indication) • RTX (does not currently have a marketing authorisation in the UK for this indication)	Established clinical management, henceforth referred to as “SoC”, in UK clinical practice, including: • OCS • Other IS agents (e.g. methotrexate, azathioprine, mycophenolate mofetil)	The appropriate comparator for this submission is a weighted average of the most used agents for the management of EGPA in UK clinical practice. Analysis of UK prescription data and clinical expert opinion indicate that the most used agents to induce and maintain remission for EGPA are OCS and IS (e.g. methotrexate, azathioprine and mycophenolate mofetil) and therefore, these are considered to form SoC in the UK.^{9,10} The treatment distribution was informed by CPRD data, which was validated by clinical expert opinion as being representative of UK clinical practice⁹ AstraZeneca does not believe that CYC and RTX are appropriate comparators for this submission, considering the different positioning of these agents in the EGPA treatment pathway, compared to the anticipated positioning of benralizumab. Specifically: • Clinical guidelines and clinical expert opinion indicate that CYC and RTX are predominantly restricted to the treatment	The exclusion of rituximab and cyclophosphamide as appropriate comparators in the CS is justified based on the population (see above). Clinical advice to the EAG indicated that neither cyclophosphamide nor rituximab are widely used in patients without severe disease. This does however represent a key concern when considered in relation to the entirety of the population as per NICE scope. Further details are provided in Section 2.2.

			of patients with severe EGPA, defined as life- or organ-threatening EGPA.⁹ Patients with life- or organ-threatening EGPA manifestations were excluded from MANDARA and therefore are not addressed within this submission - Furthermore, patients with previous CYC treatment (oral and IV use within two and three weeks of baseline [Visit 2], respectively) and patients with previous RTX treatment (within six months of study enrolment [Visit 1])^a were also excluded from MANDARA, meaning that these agents are not appropriate comparators for the purpose of this submission Additionally, CYC and RTX are not routinely used in UK clinical practice: - CYC is associated with concerns of organ-threatening toxicity and affects fertility, which are worsened by cumulative	

			doses, so clinicians are keen to restrict use to patients with severe EGPA¹¹ • As per the NHS England Clinical commissioning policy, and as substantiated by feedback from clinicians, RTX is not commonly used, and its use is likely to be greatly limited in UK clinical practice, given the restricted criteria for commissioning¹² • An analysis of CPRD data from 486 patients with EGPA, conducted in 2024, identified that CYC was only used in 2.7% of patients in England and RTX in only 1% of patients¹³ Clinical experts further validated that CYC was restricted to treating severe patients and RTX was only sparingly used in UK clinical practice, and does not form part of UK SoC⁹	

Outcomes	The outcome measures to be considered include: • Mortality • Remission rates • Total accrued duration of remission • Time to first relapse • Number of relapses • Reduction/cessation in systemic steroid use • Use of IS • Vasculitis activity scores • Pulmonary function • AEs of treatment • HRQoL	In line with final scope	N/A	Whilst the MANDARA trial encompasses a wide variety of outcomes detailed in the scope, the submission uses an ITC to assess effectiveness and nine outcomes were presented for the Bucher ITC (two of which were included in the MAIC and directly used in the cost-effectiveness modelling). This narrowing of outcomes, whilst understandable, is of some concern. Further details are provided in Section 2.3.

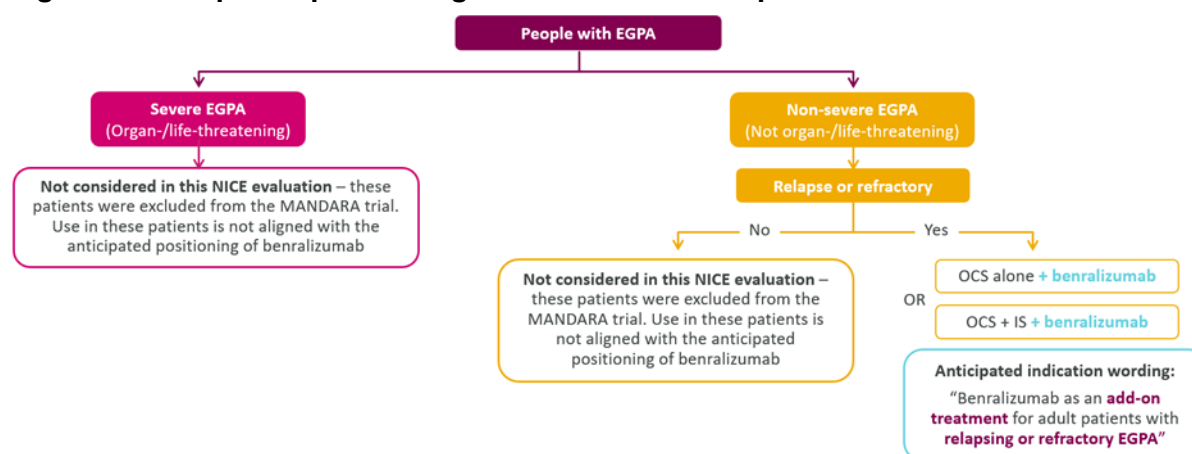
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	In line with final scope and reference case	N/A	The company submitted economic model was a state-transition EGPA model with an OCS sub-model. Incremental cost-effectiveness ratio (ICER) was used to conduct the cost-effectiveness analysis, for a sufficient time horizon. See Section 4.2 Costs were appropriately sourced from National Health Service (NHS) and Personal Social Services (PSS) perspective. Details in 0.

	The availability and cost of biosimilar and generic products should be taken into account			
Subgroups to be considered	None			
Special considerations including issues related to equity or equality	None			
Source: Table 1, Document B⁵ Footnotes: a Patients must have also shown recovery of peripheral B-cell count to within the normal range Abbreviations: CS= company submission; AE= adverse event; CPRD= Clinical Practice Research Datalink; CYC= cyclophosphamide; EGPA= eosinophilic granulomatosis with polyangiitis; HRQoL= health related quality of life; IS= immunosuppressant; ITC= indirect treatment comparison; MAIC = matching-adjusted indirect comparison; N/A= not applicable; NHS= National Health Service; NICE= National Institute for Health and Care Excellence; OCS= oral corticosteroids; PSS= Personal Social Services; RTX= rituximab; SoC= standard of care; UK= United Kingdom.				

2.1 Population

The population defined in the NICE scope is adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy.¹⁴ The population outlined in the CS is said to be 'in line with final scope'. However, the MANDARA and MIRRA trials exclude patients with organ or life-threatening EGPA (hereafter referred to as severe EGPA) < 3 months prior to screening (see Table 13, Appendix D).¹⁵ With regard to the MANDARA's trial inclusion criteria, the company report that MANDARA was designed to be a head-to-head, non-inferiority study to mepolizumab, which was anticipated to be the standard of care when benralizumab would be entering clinical practice (question A9).¹⁶ The restriction to less severe patients is linked to the company's statement that cyclophosphamide and rituximab are inappropriate comparators in the decision problem scope as they are predominantly restricted to the treatment of patients with severe EGPA (see Section 2.2).⁵ During the Factual Accuracy Check (FAC),¹⁷ the Company reiterated the positioning of benralizumab for patients with non-severe (defined as not organ- or life-threatening) EGPA (Figure 2.1).¹⁷

Figure 2.1: Proposed positioning of benralizumab for patients with EGPA



Source: Factual accuracy check and confidential information check¹⁷
Abbreviations: IS = immunosuppressant; OCS = oral corticosteroid.

The management of EGPA takes a severity-based approach, whereby EGPA severe disease is usually defined as life-threatening manifestations and/or organ impairment associated with long-term poor prognosis.¹⁸ EGPA is a rare type of ANCA-associated vasculitis (AAVs) that causes inflammation of small and medium-sized blood vessels. AAV severity is assessed with two main tools: BVAS and the Five-Factor Score (FFS).^{19,20} FFS (1994) comprises clinical manifestations at the time of diagnosis, renal insufficiency (serum creatinine >1.58 mg/dl), proteinuria >1 g per day, cardiomyopathy, gastrointestinal involvement and central nervous system (CNS) involvement.²¹ The subsequent revised FFS (2009) included age >65 years as a poor prognostic factor and removed CNS involvement.²⁰ Recent evidence-based guidance, developed by a panel of European experts, for the diagnosis and management of EGPA, also highlights that peripheral neuropathy and other rare manifestations (for example alveolar haemorrhage) should be considered when choosing remission-induction strategies.²²

CPRD data from AstraZeneca in the CS highlight that ■■■ of patients with EGPA had an FFS (1996) of 0, which is used in the budget impact model as a proxy for the proportion of non-

severe patients.⁸ Potentially therefore, restricting the population to non-severe patients excludes approximately a [REDACTED] of patients with EGPA. Clinical advice to the EAG indicated that benralizumab would also benefit the population with severe disease who are more likely than the wider EGPA population to be receiving treatment with cyclophosphamide and, to a lesser extent, rituximab. The EAG are not aware of any data from MANDARA or the CRPD that looks at fluctuations in patient-level data over the duration of the trial in relation to severity. There is however evidence from a post-hoc analysis of pooled treatment groups from MANDARA, which based on the severity of patients' prior EGPA-associated cumulative manifestations (>3 months prior to study enrolment), highlighted adjusted rates of remission were similar regardless of disease severity history.²³

At baseline in MANDARA, 45 patients in the benralizumab arm (64.3%) had relapsing disease (66% for the overall trial population).⁵ Based on clinical advice to the EAG, it is possible that relapses (either during the trial or after follow up) might be severe enough to instigate organ or life threatening disease manifestations, and therefore there is a possibility that the proportion of patients who would be eligible for benralizumab using the MIRRA/MANDARA criteria would increase over time. Clinical advice to the EAG suggests patients with severe disease would likely benefit from treatment with benralizumab based on experience with those eligible due to their concomitant severe eosinophilic asthma and experience with other IL-5 antagonists. Whether the treatment benefit with benralizumab in these patients is comparable to that in patients receiving treatment for milder disease was harder to quantify but it was noted that patients with severe disease may have very limited effective conventional treatment options.

Evidence from subgroup analysis in the MANDARA trial and the CALIMA trial (which assessed benralizumab as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma) suggests a non-significant trend towards greater improvement in patients with more severe disease (see Table 2.2 below and Table 3 in Appendix E of the CS).²⁴ Specifically from the CALIMA trial, patients who had experienced more than three exacerbations in the previous year (i.e., greater asthma severity at baseline) had a trend towards greater effects of benralizumab treatment.²⁵ This analysis showed significance, although the difference between subgroups was non-significant. Further post-hoc analysis demonstrated a 26% risk reduction (rate ratio versus placebo 0.74 (0.51 to 1.09)) for patients who had two prior exacerbations (for benralizumab 30 mg Q4W versus placebo) compared to a 45% risk reduction for patients with three or more exacerbations (rate ratio versus placebo 0.55 (0.37 to 0.81)).²⁵ The MIRRA trial also showed a subgroup effect in a priori analyses which indicated larger effects of mepolizumab in patients with more severe disease, which may imply a similar effect in other IL-5 antagonists (see Section 3.2.2 for further discussion).

Table 2.2: Annual asthma exacerbation rate ratio at 56 weeks showing subgroup analysis by exacerbations in the previous year (data from the CALIMA trial for patients with severe, uncontrolled, eosinophilic asthma).

Number of exacerbations in the previous year ¹	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)

Source: FitzGerald et al., 2016 (Appendix 17, Supplementary Appendix)²⁵

Footnotes: ¹ Annual asthma exacerbation rate ratio at 56 weeks by exacerbations in the previous year for benralizumab 30 mg Q4W versus placebo for patients receiving high-dosage inhaled corticosteroid/long-acting β 2-agonist with blood eosinophils ≥ 300 cells/ μ L
Abbreviations: CI= confidence interval

Whilst the NICE scope details adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy,¹⁴ the MANDARA/MIRRA trials included only patients without life-threatening or organ-threatening disease (hereinafter referred to as non-severe EGPA)(see Table 14, CS Appendix D¹⁵). Since there is no trial evidence available for the most severe patients in this indication and at the indicated dose for EGPA, the EAG is unable to comment on the risk/benefit ratio for patients with recent severe disease. There is however evidence that the use of benralizumab in patients with more severe, eosinophilic asthma at baseline had the greatest effect of treatment.²⁵ The eligibility criteria in MANDARA are likely to have excluded approximately a [REDACTED] of patients in the UK; those with current/recent organ or life-threatening relapsed disease at baseline.⁸ Those patients with severe disease are also unlikely to be a stable cohort over time, rather those meeting this criterion will change as patients fluctuate between disease stages (including severe relapse). If the MANDARA trial inclusion criteria were adopted in real-world clinical practice, the proportion of EGPA patients eligible for benralizumab will likely increase as patients previously severe become eligible as their disease stabilises, and patients whose disease has relapsed with organ- or life-threatening manifestations may not meet the proposed stopping criteria to withdraw treatment. Future trials (or real-world evidence) should disaggregate data for both severe and non-severe populations to illuminate efficacy by disease severity.

2.2 Comparators

The comparators reported in the NICE scope included OCS, cyclophosphamide, IS and rituximab (none of which have marketing authorisation for this condition).¹⁴ There are currently no licensed treatments for EGPA in the UK. Mepolizumab, the comparator in the benralizumab trial, has a marketing authorisation for EGPA amongst other conditions, but has no NICE guidance for this indication.²⁶ No recent UK guidelines are available for EGPA, although there are evidence-based 2023 European guidelines for EGPA²² and 2014 guidelines available from the British Society of Rheumatology for the management of AAVs, which is the group of autoimmune diseases which EGPA falls into.²⁷ Patients with a worse prognosis (e.g., FFS ≥ 1) are typically treated with a combination of IS and OCS therapy, while those with milder disease (FFS = 0) may be managed using OCS monotherapy.²⁸ OCS/IS combination therapy is also recommended as a first-line treatment for patients experiencing organ- or life-threatening manifestations, such as eosinophilic alveolitis, alveolar haemorrhage, or severe peripheral neuropathy.²⁹

As highlighted in the CS, for the non-severe patients eligible for and recruited to the MANDARA trial, who do not have organ or life-threatening EGPA <3 months prior to screening, cyclophosphamide and rituximab are unlikely to be prescribed. The CS highlights the CRPD dataset which reports only [REDACTED] patients (1.0%) had rituximab and [REDACTED] patients (2.7%) had cyclophosphamide.^{5,8} Clinical advice to the EAG supports these figures, suggesting that neither cyclophosphamide nor rituximab is widely used in patients without severe disease and also that cyclophosphamide is used more than rituximab in EGPA disease with major organ involvement as there is limited trial evidence for EGPA specifically (as trials have combined

patient populations with Granulomatosis with polyangiitis (GPA) diseases as a whole). However in severe disease with major organ involvement, cyclophosphamide is recommended for remission-induction in life-threatening disease and/or those with poor prognosis (FFS ≥ 1),³⁰ as it has been shown to be associated with adverse events related to infections, neutropenia and long-term cancer risk.³¹ Rituximab has been shown to be an effective alternative treatment, especially in situations where cyclophosphamide use may be problematic (relapse after cyclophosphamide, women of childbearing age, risk of malignancy),³² but there are strict criteria governing its use as detailed in the NHS England Clinical Commissioning Policy.^{5,12}

Mepolizumab, a humanised anti-interleukin-5 (anti-IL-5) monoclonal antibody is the comparator in the MANDARA trial and is a NICE recommended add-on treatment for severe refractory eosinophilic asthma.^{6,33} Whilst mepolizumab has a UK marketing authorisation as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA, there is no NICE recommendation as GlaxoSmithKline did not provide an evidence submission.³⁴ CPRD prescription rates provided by AstraZeneca highlight [REDACTED] with EGPA received mepolizumab.⁸

Whilst EGPA patients may be treated by IS (including cyclophosphamide), OS and biologics (rituximab and mepolizumab), for those patients with non-severe disease, IS and OCS are appropriate comparators to benralizumab in the CS. The MANDARA trial prohibited cyclophosphamide and rituximab in the weeks/months before screening/baseline (see Section D.1.6).¹⁵ [REDACTED] Assuming the focus is on patients with non-severe EGPA disease, the EAG are satisfied that only OCS and IS are appropriate comparators. However, for the population of patients with EGPA more widely, cyclophosphamide and rituximab may be appropriate additions or alternatives to IS as part of comparator treatment in some instances for the patients with severe disease (see Section 3.3.1.1 for further discussion).

2.3 Outcomes

The NICE scope encompasses a wide variety of outcomes including mortality, remission (remission rates, total accrued duration of remission), relapse (total accrued duration of remission, time to first relapse, number of relapses), treatment changes (reduction/cessation in systemic steroid use, use of IS), physiological measures (vasculitis activity scores and pulmonary function), adverse events and HRQoL. Whilst the company states that the outcomes reported in the CS are in line with this scope, it is important to highlight that this reporting refers only to the MANDARA trial. As the submission uses an indirect treatment comparison (ITC) to assess effectiveness, nine outcomes were presented for the Bucher ITC related to remission, relapse and OCS dosage.

Two outcomes were modelled for the matching-adjusted indirect comparison (MAIC) (see Table 2.3 for a comparison of the outcomes reported for MANDARA, MIRRA and the ITC/MAIC). Two of the seven Bucher ITC outcomes were used in the cost-effectiveness modelling (the same two outcomes were validated in the MAIC); namely the proportion of patients in remission at weeks 36 and 48 together with the annualised relapse rate that are reported in both the Bucher ITC and MAIC.

Table 2.3: Summary of outcome data in the MANDARA and MIRRA trials and in the indirect treatment comparisons

Outcome type	NICE Scope	MANDARA	MIRRA ^{d,e}	Bucher ITC	MAIC
Survival	Mortality	Reported in AEs	Reported in AEs	No comparable outcome	No comparable outcome
Remission	Remission rates	Remission rate at weeks 36 and 48 (primary outcome) -Main remission ^a -OCS dose -BVAS=0	Number of patients who are in remission at 36 and 48 weeks	Proportion of patients in remission at both week 36 and 48 (main remission definition) ^c	Proportion of patients in remission at both week 36 and 48 (main remission definition)
				Proportion of patients in remission at both week 36 and 48 (supporting remission definition) ^c	No comparable outcome
	Total accrued duration of remission	Number of patients in each category of accrued duration of remission	Number of patients in each category of accrued duration of remission	Total accrued duration of remission over a 52-week period (main remission definition)	No comparable outcome
				Total accrued duration of remission over a 52-week period (supporting remission definition)	No comparable outcome
		Remission within the first 24 weeks and remaining in remission for the remaining of the double-blind period	Remission within the first 24 weeks and remaining in remission for the remaining of the treatment period	Proportion of patients who achieved remission within the first 24 weeks and stayed in remission until 52 weeks (main remission definition)	No comparable outcome

Outcome type	NICE Scope	MANDARA	MIRRA ^{d,e}	Bucher ITC	MAIC
				Proportion of patients who achieved remission within the first 24 weeks and stayed in remission until 52 weeks (supportive remission definition)	No comparable outcome
Relapse	Time to first relapse	Time from randomisation to first EGPA relapse	Time to first EGPA relapse	Time to first EGPA relapse	No comparable outcome
	Number of relapses	Annualised relapse rate	Annualised relapse rate	Annualised relapse rate ^c	Annualised relapse rate
		Annualised major relapse rate	Annualised major relapse rate	No comparable outcome	No comparable outcome
Treatment changes	Reduction/cessation in systemic steroid use	Average daily prednisolone/prednisone dose during weeks 48 through 52 (in different categories, see clinical trial record ³⁶	Average daily prednisolone/prednisone dose during the last 4 weeks of the study treatment period	Average daily OCS dose during the last 4 weeks of the study *weeks 48 through 52)	No comparable outcome
	Use of IS	No comparable outcome	No comparable outcome	No comparable outcome	No comparable outcome
Clinical benefits		Proportion of patients who have achieved any clinical benefit (i.e., when meeting any of the criteria reported in footnote ^b). Proportion of patients who have achieved complete response when meeting all of the criteria.	No comparable outcome	No comparable outcome	No comparable outcome

Outcome type	NICE Scope	MANDARA	MIRRA ^{d,e}	Bucher ITC	MAIC
Symptom changes		Change from baseline in ACQ-6	No comparable outcome	No comparable outcome	No comparable outcome
		Change from baseline in sino-nasal symptoms (SSQ)	No comparable outcome	No comparable outcome	No comparable outcome
		Change from baseline in SNOT-22	No comparable outcome	No comparable outcome	No comparable outcome
		Proportion of PGIC responders at each weekly assessment	No comparable outcome	No comparable outcome	No comparable outcome
Physiological outcomes	Vasculitis activity scores	Change from baseline in VDI	No comparable outcome	No comparable outcome	No comparable outcome
		Change from baseline in BVAS	No comparable outcome	No comparable outcome	No comparable outcome
		Change from baseline in blood eosinophil counts	No comparable outcome	No comparable outcome	No comparable outcome
	Pulmonary function	Change from baseline in pulmonary function	No comparable outcome	No comparable outcome	No comparable outcome
Adverse events	AEs of treatment	Numbers of participants with AEs and SAEs	Number of patients with local and systemic AEs	No comparable outcome	No comparable outcome
HRQoL/ wellbeing	HRQoL	Change from baseline in SF-36v2	No comparable outcome	No comparable outcome	No comparable outcome
		Change from baseline in WPAI	No comparable outcome	No comparable outcome	No comparable outcome

Source: NICE scope;¹⁴ CS Section B.2.6.1 and B.2.6.2;⁵ CS Table 15, Appendix D;¹⁵ MANDARA clinical trial record;³⁶ MIRRA clinical trial record³⁷

Footnotes: ^a Main remission was defined as BVAS = 0 and OCS dose ≤4 mg/day (in the event a patient reached remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission). Supportive remission is defined as BVAS = 0 and OCS dose ≤7.5 mg/day.

^b (i) Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the double-blind treatment period; (ii) ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52 and (iii) EGPA relapse free during the double-blind treatment period.

^c Informs cost-effectiveness modelling

Outcome type	NICE Scope	MANDARA	MIRRA ^{d,e}	Bucher ITC	MAIC
^d Only those trial outcomes in MIRRA that directly mapped to the MANDARA trial are reported. ^d Full list of MIRRA outcomes:³⁷Primary outcomes include: number of participants in each category of accrued duration of remission and number of participants who are in remission at 36 and 48 weeks. Secondary outcomes include: time to first EGPA relapse; number of participants in each category of average daily prednisolone/prednisone dose during the last 4 weeks of the study treatment period; number of participants who achieved remission within the first 24 weeks and remained in remission for the remainder of the treatment period; number of participants in each category of accrued duration of remission; number of participants who are in remission at 36 and 48 weeks; number of participants who achieved remission (BVAS=0 and prednisolone/prednisone <=7.5 mg/day) within the first 24 weeks and remained in remission for the remainder of the treatment period; number of participants with local and systemic AEs; change from baseline in clinical chemistry parameters of Alanine Aminotransferase (ALT), Alkaline Phosphatase (Alk.Phosph.), Aspartate Aminotransferase (AST), Creatinine Kinase, Gamma Glutamyl Transaminase (GGT) and Lactate Dehydrogenase (Dehydro) levels; change from baseline in clinical chemistry parameters of albumin and protein levels; change from baseline in clinical chemistry parameters of direct, indirect and total bilirubin and creatinine levels; change from baseline in calcium, chloride, cholesterol, glucose, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, phosphorus, potassium, sodium, urea nitrogen and very low density lipoprotein (VLDL) cholesterol levels; change from baseline in clinical chemistry parameter of troponin levels; change from baseline in haematology parameters of basophils, eosinophil, leukocytes, lymphocytes, monocytes, neutrophils, platelets levels; change from baseline in haematology parameters of Mean Corpuscle Haemoglobin Concentration (MCHC) and haemoglobin levels; change from baseline in haematology parameters of Mean Corpuscle Volume (MCV) levels, change from baseline in haematology parameters of Mean Corpuscle Haemoglobin (MCH) levels; change from baseline in haematology parameters of erythrocytes levels; number of participants with anti-mepolizumab antibodies; change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels; change from baseline in pulse rate; change from baseline in body temperature; mean change from baseline in QT Interval Corrected by Fridericia's method (QTcF) and QT Interval Corrected by Bazett's method (QTcB) values and maximum change from baseline in QTcF and QTcB values. Abbreviations: AE= adverse event; ACQ-6= Asthma Control Questionnaire (6-item version); EGPA= eosinophilic granulomatosis with polyangiitis; BVAS= Birmingham Vasculitis Activity Score; IS= immunosuppressant; ITC= indirect treatment comparison; MAIC= matching-adjusted indirect comparison; PGIC= Patient Global Impression of Change; OCS= oral corticosteroids; SNOT-22= Sino-nasal Outcome Test-22; SSQ= Sino-nasal Symptoms Questionnaire; SF-36v2= Short Form 36-item health survey (version 2, acute recall); VDI= Vasculitis Damage Index; SAE= serious adverse event; WPAI= Work productivity and Activity Impairment Questionnaire; HRQoL= health-related quality of life.					

The NICE scope encompassed a much broader range of outcomes than that presented in the Bucher ITC, which listed nine outcomes, two of which were incorporated into the cost-effectiveness analysis (sensitivity analysis in the cost-effectiveness modelling used the results of a MAIC in addition). The outcomes utilised in the ITC (remission, relapse and OCS dosage) incorporate definitions that use vasculitis activity scores, pulmonary function, and use of IS, which are also listed in the NICE scope. However, this comes with the caveat that the clinical effectiveness of benralizumab related to these outcomes must be derived from other outputs. Furthermore, in the CS Section B.3.4 the company reported on the limitations of SF-36 used in MANDARA to assess HRQoL including its inability to fully capture the symptom burden of EGPA and the loss of validity when mapped to EQ-5D.⁵ To inform the HRQoL data, two studies were conducted to generate more robust and accurate data to inform the cost-effectiveness analysis (the Adelphi DSP study and UK-specific vignette study)^{5,38} For further discussion see Section 4.2.6.

The EAG acknowledges that the two key outcomes presented (proportion of patients in remission (main remission definition) at both week 36 and week 48 and the annualised relapse rate) are the most insightful for the model. The Bucher ITC results for the average daily OCS dose during the last 4 weeks of the study are also informative and are included in the NICE scope.

2.4 Special considerations including issues related to equality

The use of benralizumab in the CS was shown to reduce OCS dose relative to standard of care (Bucher ITC average daily OCS during the last 4 weeks of the study was OR (95% CI): [REDACTED]).¹⁵ Tapering of OCS to the minimum effective dosage reduces long-term-toxicity, and the reduction of IS is preferable to limit the risk of complications, especially infections.²² This is particularly important to older people (aged >65 years), given their increased vulnerability to infectious diseases and increased burden of comorbidities. If OCS dose were reduced, this could be particularly beneficial to older people.

However, the restriction to non-severe patients included in the MANDARA and MIRRA trials might inadvertently restrict treatment with benralizumab to slightly younger patients. Clinical advice to the EAG suggests patients with severe disease are likely to be older. As such, this has the potential to increase inequalities.

The CPRD data highlights that only [REDACTED]% and [REDACTED]% of patients with EGPA are under 35 or between 35 and 49 years respectively.⁸ There also appear to be [REDACTED] in both the CPRD data and the MANDARA trial (question A11, Points for Clarification (PfC)).^{8,16} The known adverse effects OCS exposure during pregnancy can have on the mother and newborn,³⁹ suggests the proportion of younger female patients of child-

¹ The categories for average daily OCS dose during the last four weeks of the study (weeks 48 through 52) are: 0 mg, > 0 to ≤ 4 mg, > 4 to ≤ 7.5 mg, and > 7.5 mg (Table 16, CS Appendix D)¹⁵ AstraZeneca plc. *Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]. Single technology appraisal. Company evidence submission: Appendix D.* Cambridge, UK: AstraZeneca plc; 2024.

bearing age with EGPA may be at particular risk. Therefore, a treatment which reduces the use of OCS may be particularly beneficial for these younger, female patients.

Clinical advice to the EAG suggests that the inequalities associated with age and sex may not interact: although older patients are more likely to have severe disease, female and male patients are equally likely to present with severe disease although >50% of the patient population as a whole is female.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify evidence on the efficacy and safety of treatments for EGPA. The methods of the SLR are detailed in Appendix D of the CS.¹⁵ The company states the protocol for the SLR was developed de novo, in accordance with the methodological principles of conduct for SLRs as detailed in the University of York Centre for Reviews (CRD) and Dissemination's "Guidance for undertaking Reviews in Health Care".⁴⁰ A summary of the EAG's critique of the methods used by the company to identify evidence relevant to the decision problem is presented in Table 3.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D, Section D.1.1, p.8-10 ¹⁵	Appropriate The range of sources searched by the company was appropriate. Although the reference lists of relevant systematic reviews/(network) meta-analyses were searched for relevant records, there is no mention of searching the reference lists of included studies which is usually considered good practice. As a range of other sources were searched the EAG do not consider that this would have resulted in potentially relevant studies being missed.
Search strategies	Appendix D, Section D.1.1, p.11-32 ¹⁵	Some concerns The searches rely heavily on a set of condition-related search terms. This set of terms could have been broadened to increase sensitivity of the search by the inclusion of terms related to the intervention and by allowing for plurals and differing word orders. See Section 5.1.2 for more details.
Search filters	Appendix D, Section D.1.1, p. 11-32 ¹⁵	Appropriate Search filters adequately captured the decision problem. (In response to the clarification letter, question A1, ¹⁶ the company stated that the search filters used were those designed by Cochrane (Cochrane Highly Sensitive Search Strategy for identifying RCTs) ⁴¹ and the Scottish Intercollegiate Guidelines Network (SIGN) (observational studies)). ⁴²
Eligibility criteria	Appendix D, Section D.1.2, p.28-29 ¹⁵	Some concerns The SLR eligibility criteria overall aligned with that specified in the NICE scope. ¹⁴ The EAG are satisfied with the predefined eligibility framework for the population/intervention/comparator/outcomes. However, there are some concerns with the study design and the company's prioritisation strategy. These are further described in Section 3.1.3.

Screening	Appendix D, Section D.1.2 p.27; D.1.3, p.30-32 ¹⁵	Appropriate Screening was done in duplicate, with disagreements resolved by a third reviewer. The flow of records through the original SLR and update were presented in an accompanying PRISMA flow diagram (Figure 1 in Appendix D). ¹⁵ In total 41 publications reporting on 12 studies were included (RCTs: n=8; non-RCTs: n=2; single-arm study: n=1, RCT and non-RCT: n=1) A complete list of excluded studies with rationale for exclusion was provided in the data extraction table embedded in Appendix D. ¹⁵
Data extraction	Appendix D, Section D.1.2, p.27-28 ¹⁵	Appropriate Data extraction was performed by a single investigator into a pre-specified data extraction grid in Excel and verified by a second investigator. Any discrepancies were resolved by consulting a third individual. ¹⁵ The company are the sponsor of the only identified clinical trial from the SLR which assessed the intervention in line with the NICE scope, and therefore have direct access to the clinical trial data. The EAG agree data extraction methods used were appropriate.
Quality appraisal	Appendix D Section D.1.2, p.30 ¹⁵	Appropriate All included studies were assessed by one individual and verified by a second independent reviewer. Non-RCTs were assessed using the Joanna Briggs Institute critical appraisal for quasi-experimental studies, while the quality assessment tool developed by the University of York CRD for RCTs, and recommended by NICE, ⁴⁰ was performed for the main publication of each RCT included. The EAG deem the approaches taken appropriate.
Abbreviations: CRD= Centre for Reviews and Dissemination; CS= company submission; EAG= Evidence Assessment Group; NICE= National Institute for Health and Care Excellence; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT= randomised controlled trial; SLR= systematic literature review; SIGN= Scottish Intercollegiate Guidelines Network.		

3.1.1 Search methods for the clinical effectiveness SLR

The company conducted separate searches for clinical effectiveness studies (presented in the CS Appendix D),¹⁵ and cost effectiveness, HRQoL and cost and resource use studies (CS Appendices G, H and I respectively).⁴³⁻⁴⁵ The EAG used the PRESS checklist to appraise the search strategies.⁴⁶ In this section, we present the critique of the search methods for clinical effectiveness studies. The critique of searches for cost effectiveness studies, HRQoL studies and cost and resource use is presented in Section 4.1.1. As some of the issues were the same for all the searches there are cross references to the relevant section to avoid repetition. The searches were first run in June 2023 and were updated in August 2024 and so are considered up to date.

3.1.2 Search strategies

The searches were based on a set of terms related to the condition with the application of a study design (or research type) search filter(s) in some of the electronic bibliographic databases. Terms for the intervention were not included in the search strategies. The set of

condition-related search terms needed to be as sensitive as possible in order to avoid potentially missing relevant studies. The sensitivity of the search could have been increased by allowing for plurals such as 'granulomatoses', '(poly)angiitides' or 'vasculitides'. Only one instance of proximity searching was used meaning that for the remaining phrases the terms had to appear in the order given with no words allowed in between. It may have been worth considering adding the slightly broader controlled vocabulary terms/subject headings to increase the sensitivity e.g. the MeSH term 'Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis', additional to the very specific subject headings used, to allow for less precise application of subject headings within an electronic database. No specific searches for adverse effects of the intervention were conducted. These considerations led to some concerns as to whether potentially relevant studies may have been missed by the searches. However, these concerns were mitigated by the range of other sources searched including grey literature and reference lists of relevant systematic reviews.

3.1.3 Eligibility criteria

The SLR predefined eligibility criteria are presented in Table 3.2 (section D.1.2, Table 10)¹⁵ and overall were in line with that specified by the NICE scope.¹⁴ The EAG are satisfied with the predefined eligibility framework for the population/intervention/comparator/outcomes, however, there are some concerns with the study design and company's prioritisation strategy for inclusion.

The company initially kept the inclusion criteria broad and adopted an evidence prioritisation strategy which determined that only RCTs and interventional non-RCTs should be prioritised and included in the review for extraction, whilst observational (non-interventional) studies should be deprioritised. The company justified their reasons for prioritisation in section D.1.2,¹⁵ ensuring only the highest quality and relevant evidence was identified and considered for inclusion in the indirect treatment comparison (ITC). Although subject to a higher risk of bias, observational studies may provide supplemental data and real-world evidence such as on the natural history of the condition and treatment patterns, to help contextualise RCT results. It may therefore have been beneficial to have included these studies to check for overall generalisability and robustness of the evidence presented. As part of this submission the company provided additional data including the Adelphi Real World DSP³ and qualitative insights from patients⁴⁷ and clinical experts.⁹

Furthermore, according to the CS Section D.1.3 which includes the PRISMA diagram,¹⁵ there were in total 37 publications in the SLR update and 29 publications in the original SLR with a non-interventional study design, and therefore excluded as part of the company's prioritisation strategy. However, as reported in the data extraction workbook, provided by the company (embedded in Appendix D, section D.1.4),¹⁵ a further 31 observational study congress abstracts were also deprioritised in the original SLR but this step was not included in the PRISMA diagram nor stated in the CS section D.1.3.¹⁵ The EAG note these excluded scientific abstracts comprised study abstracts linked to full text records also screened by the company, and abstracts without linked full text publications, which may have provided further supportive evidence as discussed above regarding the inclusion of observational studies.

In the CS section D.1.2 (Table 10),¹⁵ publication types included peer-reviewed publications and conference abstracts (published in or after 2013). Clinical trial registries were also included but were only used as a supplement for data from published literature. Post-hoc analyses were formally included but were not data extracted, as part of the company's

prioritisation strategy (section D.1.2).¹⁵ There were three post-hoc analyses of the MIRRA trial; these provided support for clinical benefit from mepolizumab treatment relative to SoC in patients with EGPA, irrespective of baseline clinical characteristics (refractory disease status, IS use, EGPA duration, number of relapses, and OCS dose),⁴⁸ and whether patients presented with or without a predominantly vasculitic phenotype.^{49,50} Additionally there was one post-hoc analysis of the MANDARA trial, indicating clinical benefits from either benralizumab or mepolizumab treatment for patients with EGPA, irrespective of ANCA status.⁵¹ Post-hoc analyses warrant caution in their interpretation as they can be data-driven, lack statistical power, and subject to multiplicity concerns. The EAG agree the four included post-hoc analyses provide supportive evidence but also agree with the company's approach to de-prioritise the data generated from these in their submission.

Systematic reviews were excluded, although the bibliographies of systematic reviews and meta-analyses were searched for relevant primary studies that were not found through database searches; in total four systematic reviews were searched. The EAG agree this approach to the selection of publication types ensures the most reliable and high-quality data are included and therefore deem the approach to be appropriate.

Lastly, the company stipulated studies were limited to English language only at full text and limited to years 2003 onwards (Table 10, Section D.1.2).¹⁵ Whilst language and time restrictions are more subject to bias, the EAG agree that, considering no non-English language records were reported to be excluded at full-text, the rarity of the disease and the treatments available, removing these restrictions would likely not have provided any further relevant evidence.

Table 3.2: Eligibility criteria for the identification of studies to be included in the SLR

Domain	Inclusion Criteria	Exclusion Criteria
Patient population	Adults (≥ 18 years) diagnosed with EGPA (formerly Churg-Strauss syndrome) that are: • Treatment naïve (i.e., newly diagnosed) or • Treatment experienced (e.g., relapsed/refractory) or • Included in mixed populations of ANCA-associated vasculitis (AAV) where outcomes are reported separately for EGPA Subpopulations/subgroups: The main subgroups of interest will be: • ANCA-positive status • Eosinophilic count • Medication use at baseline • Newly diagnosed subpopulation • Relapsed/refractory subpopulation	• Paediatric patients (< 18 years) • Studies reporting exclusively patients diagnosed with granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis disease) or microscopic polyarteritis (MPA)
Intervention /comparator	Any pharmacological treatment including but not limited to: • Immunosuppressive drugs (e.g. azathioprine, methotrexate, mycophenolate mofetil) • Corticosteroids	• Non-pharmacological treatments • Treatments aiming for symptom relief only

Domain	Inclusion Criteria	Exclusion Criteria
	Targeted therapies e.g., benralizumab, mepolizumab, rituximab, omalizumab	
Outcomes	Where reported: - Response rate - Proportion of patients in remission and duration of remission - Relapse rate - Time to first relapse - Mortality - Change from baseline in eosinophilic count, VDI, BVAS, OCS dose and pulmonary function - Asthma exacerbation - Organ damage - Treatment-emergent adverse events (TEAEs) and serious adverse events (AEs) - Discontinuation due to AEs - Steroid reduction	Outcomes not listed in inclusion criteria
Study design	- RCTs - Non-RCTs - Single arm trials - Observational/real-world studies (prospective and retrospective cohort studies, case-control studies)^a	- Pharmacokinetics studies - Case series and case reports - Animal or in vitro studies
Publication type	- Peer-reviewed publications - Conference abstracts published in or after 2013 - Clinical trial registries^b	- Narrative reviews - Conference abstracts published before 2013 - Systematic reviews^c - Health technology assessments (HTA) reports/submissions - Commentaries, editorials or notes - Clinical trial protocols
Language	English language at full text	Non-English language
Other	Studies published in or after 2003	Studies published before 2003

Source: Table 10, CS appendices section D.1.2¹⁵

Footnotes: ^aObservational studies were ultimately deprioritised as part of our evidence prioritisation strategy.

^bData from clinical trial records were used to supplement data from published literature. ^cSystematic reviews and meta-analyses were used only to identify potentially relevant primary studies that have not been found through database searches. The following systematic reviews and meta-analyses were identified and bibliographies searched: Alchi, MB et al. Scand J Rheumatol. 2023 Sep;52(5):564-573; Jackson, DJ et al. Am J Respir Crit Care Med. 2024;209:A5383; Sanchez-Alamo, B et al. RMD Open. 2023 Jun;9(2):e003083; Techasatian, W et al. Heart. 2024 Apr 25;110(10):687-693.

Abbreviations: AAV= ANCA-associated vasculitis; ANCA= Anti-neutrophil cytoplasmic antibody; AE= adverse event; BVAS= Birmingham vasculitis activity score; EGPA= eosinophilic granulomatosis with polyangiitis; GPA= granulomatosis with polyangiitis; HTA= health technology assessment; MPA= microscopic polyarteritis; RCT= randomised controlled trial; TEAE= treatment-emergent adverse event; VDI= vasculitis damage index.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Two trials were included in the CS, MANDARA¹ and MIRRA,² which are summarised below. Both are international, randomised, double-blind, parallel group, Phase III trials included in the SLR as part of the CS (Section B.2.9.2, Table 19).⁵ The MANDARA trial was the only RCT identified investigating the efficacy and safety of benralizumab compared to any comparator (mepolizumab) in patients with refractory and relapsing EGPA, applicable to the NICE scope.

Because mepolizumab treatment is not a relevant comparator to the decision problem, nor a reimbursed treatment option in the UK, the company performed a feasibility assessment of all RCTs (n=8) identified in the SLR, to enable an anchored ITC. The company determined SoC in the UK to comprise OCS with or without IS, and concluded MIRRA was the only trial investigating the common comparator, mepolizumab, that would allow an indirect comparison of benralizumab with SoC (OCS with or without IS).

The company concluded that a Bucher ITC was appropriate owing to the similarity in trial design, patient populations, and outcome measurements between MANDARA and MIRRA. However, as anchored ITCs are subject to systematic bias, population adjustment methods were additionally adopted in a MAIC to validate the results from the ITC. In the CS quality assessments of the MANDARA and MIRRA trials were provided; these indicated robust trial methodologies which the EAG are overall satisfied represent rigorous assessments of the comparisons. However, the EAG recognise that the eligibility criteria for both trials exclude patients with severe EGPA, and those receiving treatment with cyclophosphamide or rituximab, indicating a lack of evidence and certainty in the clinical effectiveness and safety of benralizumab in this patient population which is within remit of the NICE scope, this is further discussed in Key Issue 1.

3.2.1 MANDARA

The pivotal trial providing clinical evidence for the effectiveness of benralizumab in patients with EGPA is the MANDARA trial (AstraZeneca) (NCT04157348).³⁶ The MANDARA trial (AstraZeneca) is an international, randomised, double-blind, active-controlled, non-inferiority study to compare the efficacy and safety of benralizumab versus mepolizumab, in 140 randomised adult patients with relapsing or refractory EGPA on OCS with or without stable IS therapy. In the benralizumab arm patients received one 30 mg benralizumab injection and three placebo to mepolizumab injections, while patients in the mepolizumab arm received three 100 mg mepolizumab injections plus one placebo to benralizumab injection.¹ Injections were administered subcutaneously every 4 weeks for 52 weeks. The trial is being conducted in 50 sites in nine countries (USA, Canada, UK, Belgium, France, Germany, Italy, Israel, Japan), and currently has an ongoing OLE period.⁵² A summary of the EAG's critique of the design, conduct and analysis of MANDARA trial is presented in

Table 3.3: Summary of EAG's critique on the design, conduct and analysis of the MANDARA trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Treatment	B.2.3.1. p30 ⁵	Appropriate MANDARA comprised 52 weeks of treatment with benralizumab 30 mg via SC injection, or mepolizumab 300 mg via 3 separate 100mg injections, every four weeks in addition to OCS with or without IS. A higher treatment dosage of benralizumab compared to that recommended for severe asthma⁶ is justified as EPGA presents as a more severe disease with a higher eosinophilic load, and corresponds to the higher mepolizumab dosage and administration for EGPA indicated by the EMC and FDA.^{33,53} The EAG agree with benralizumab as an add-on treatment to OCS, to help reduce OCS-dependence and associated toxicities.
Randomisation	B.2.3 P31, ⁵ MANDARA CSR ⁵⁴	Appropriate During the trial 140 participants were randomised from 50 sites across the USA (n=13), Canada (n=19), Japan (n=8), Belgium (n=4), France (n=33), Germany (n=17), Israel (n=10), Italy (n=18), and the UK (n=18).^{54,55} Following screening patients were stratified by region (North America, Western Europe and Japan) and randomised 1:1 to receive benralizumab (n=70) or mepolizumab (n=70) using a computerised system. Considering the distribution in patient location the EAG finds the methods of randomisation appropriate.
Allocation concealment	B.2.3 Table 5, P31-35 ⁵	Appropriate The trial used a number of measures including centralised allocation to ensure allocation of treatment was concealed to study sponsors, investigators involved in treatment and monitoring, and patients, throughout the 52-week treatment period. In conjunction with methods used to maintain blinding (outlined below), the EAG are satisfied with the measures taken.

Eligibility criteria	B.2.3 Table 5 p31-35 ⁵ ; MANDARA protocol ⁵⁶	Key issue 1 Eligible patients were aged ≥ 18 years old who had a documented EGPA diagnosis, at least 6 months prior to screening; a stable OCS dose ≥ 7.5 mg/day prednisolone/prednisone (but not >50 mg/day) for at least four weeks; and a history of relapsing or refractory disease^{a, 55}. The EAG agrees this aligns with the population in the NICE scope,¹⁴ however patients with severe EGPA were excluded. Additionally, the EAG note that prior treatment with comparators CYC and RTX listed in the NICE scope were also stated in the exclusion criteria. A key concern therefore arises over the representation of patients with severe EGPA, who may also be receiving treatment with CYC or RTX as (clinical advice to the EAG). See Section 3.2.1.1 below.
Blinding	B.2.3 Table 5 p31-35 ⁵	Appropriate To maintain blinding equal number of vaccines per treatment were administered using visually matched placebos. Special packaging and labelling were also used. Together with measures taken to conceal treatment allocation, the EAG finds these methods to maintain blinding of participants, investigators (including outcome assessors) and sponsors appropriate.
Baseline characteristics	B.2.3.2, Table 6, p. 36-37; ⁵ PfC questions A4 and A5 ¹⁶	Some concerns From 140 patients randomised, 18¹ were from four sites across the UK; (■■■■ patients were randomised to benralizumab; ■■■■ patients to mepolizumab). The demographic and disease characteristics were balanced between treatment arms; however, the reported data were not stratified by country. The EAG had concerns around the SoC provided depending on geographic location and asked the company to provide OCS and IS usage by country and UK study site in the PfC (Questions A4 and A5).¹⁶ Clinical advice to the EAG verified that baseline characteristics reflected patients with non-severe EGPA seen in UK clinical practice and did not represent patients with severe disease who may also be receiving treatment with CYC or RTX. See Section 3.2.1.2 for further comment.

Dropout rate	B.2.4.1 Fig 7, p.38; ⁵ MANDARA OLE Interim results; ⁴ Specks et al., 2024 ⁵²	Appropriate From 140 patients randomised, 136 patients completed the double blind 52-week treatment period. Patients who completed the double-blind period could enrol in the OLE; in total 128 patients have enrolled onto the ongoing OLE ⁵². [REDACTED] [REDACTED] The EAG have no concerns over the retention rate.
Statistical analyses	B.2.4.2, Table 8, p. 39; ⁵ MANDARA CSR ⁵⁷	Appropriate To demonstrate noninferiority of benralizumab to mepolizumab a prespecified margin of -25% at the one sided 2.5% significance level was used. A sample size of 140 was estimated to provide approximately 90% power. All efficacy endpoints were assessed using all patients who were randomised and received at least one dose of treatment. Safety analysis included all patients who received at least one dose of investigational product. Sensitivity analyses using the per-protocol population were provided by the company in the CSR. The EAG finds the statistical analysis approach appropriate.

Outcome measures	B.2.3 p31-35, Table 5, ⁵; Appendix D.1.6 p46-49;¹⁵ MANDARA CSR⁵⁷	Appropriate Recommended definitions and clinically validated instruments for assessing EGPA were used to evaluate primary and secondary outcomes also listed in the NICE scope. The primary outcome was main remission (BVAS = 0 and OCS dose ≤ 4 mg/day at both Weeks 36 and 48). A supportive endpoint for remission recommended by the European League Against Rheumatism (EULAR), which uses an attained OCS dose of ≤7.5 mg/day, was also applied.⁵⁸ Other outcomes included total accrued duration of remission, time to first relapse, number of relapses, reduction in OCS use, use of IS, annualised relapse rate, vasculitis activity scores, pulmonary function and HRQoL. Safety and tolerability outcomes including AEs leading to discontinuations and deaths were also evaluated. Although the HRQoL instrument used was not deemed accurate for EGPA in the CS, the EAG note the [REDACTED] and the company's additional undertaking to collect more robust HRQoL evidence (for further discussion see Section 4.2.6). Overall, the EAG considers the outcomes to be appropriate.

Results: Efficacy outcomes	B.2.6.1, p42-52; Appendix N p152-160; PfC question A12;¹⁶ MANDARA OLE Interim results;⁴ MANDARA CSR⁵⁷	Appropriate The trial met the primary endpoint with benralizumab showing non-inferiority to mepolizumab: add-on treatment with benralizumab resulted in remission in 57.7% of patients at both Weeks 36 and 48, compared with 56.5% with mepolizumab (treatment difference of 1.2% (95% CI: -14.1, 16.5; p=0.8773)). Secondary endpoints also supported noninferiority between treatment arms and interim results of the MANDARA OLE indicated durability of response to benralizumab treatment beyond the 52-week double blind period. The company also notes a stopping criterion in the form of a response assessment conducted at 52 weeks in the economic model, consistent with the recommended use of benralizumab in severe asthma and in line with the recommended use of benralizumab in EGPA in UK clinical practice^{6,9} (detailed in question A7 of the PfC).¹⁶ In the MANDARA OLE, there are [REDACTED] patients who stopped treatment with benralizumab due to lack of efficacy ([REDACTED]).⁴ Overall, the EAG agrees that the efficacy results presented is appropriate.

Results: Adverse events	B.2.10, p.55-63; Appendix F;⁵⁹ PFC question A10;¹⁶ MANDARA OLE Interim results;⁴ MANDARA CSR⁵⁷	Appropriate Benralizumab was demonstrated to be well tolerated with no new safety concerns. Duration of exposure to the IP between treatment arms was similar. Treatment related AEs were also comparable (████ vs █████ for those receiving benralizumab compared to mepolizumab). Owing to the drug mechanism of action targeting eosinophils, helminth infections and malignancy were AEs of interest. While no helminth infections were reported, across the double-blind and OLE period, 5 malignancies, unrelated to the IP were reported. No AEs led to discontinuation in patients receiving benralizumab during the double-blind period, while two patients receiving mepolizumab discontinued due to AEs not related to treatment. No deaths were reported during the double-blind period. One death was reported during the OLE; however, it was considered unrelated to treatment.⁵ Overall the EAG consider the safety profile of benralizumab in this patient population is acceptable.
Subgroup analysis	Appendix E p.56-57; ²⁴ MANDARA CSR; ⁵⁷ Appendix E²⁴	Appropriate No subgroup analysis was specified in the NICE scope.¹⁴ However, the company as part of this submission demonstrated the efficacy of benralizumab compared with mepolizumab on the primary endpoint to be consistent across multiple prespecified subgroups. Considering the heterogeneity of EGPA clinical manifestations and small sample sizes, the EAG agree the subgroup analysis provides additional supportive evidence for consistent efficacy in the included population but should be interpreted cautiously.

Footnotes: aPatients had to have a history of relapsing or refractory disease, defined as: Relapsing disease: Patients must have a history of at least one confirmed EGPA relapse (i.e., requiring an increase in the investigator-initiated OGC dose, initiation/increased dose of immunosuppressive therapy or hospitalization) within the past 2 years, which occurred ≥ 12 weeks prior to screening (visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day. Japan-only definition of relapsing disease: Patients must have had a past history of at least one confirmed EGPA relapse (i.e., requiring an increase in the investigator-initiated OGC dose, the initiation of intravenous (IV) prednisolone (or equivalent), initiation/increased dose of immunosuppressive therapy, initiation/increased dose of IV immunoglobulin or hospitalisation) within the past 2 years, which occurred ≥ 12 weeks prior to screening (visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day. Refractory disease: Either failure to attain remission within the 6 months prior to visit 1 (BVAS [scale 0–63] = 0 and OGC dose ≤ 7.5 mg/day prednisolone or equivalent) following induction treatment with a standard regimen, administered for ≥ 3 months; OR within 6 months prior to screening (visit 1), recurrence of symptoms of EGPA (not necessarily meeting the protocol definition of relapse) while tapering OGC, occurring at any dose level ≥ 7.5 mg/day prednisolone or equivalent.^{55,56}

Abbreviations: SC = subcutaneous; OCS = oral corticosteroid; IS = immunosuppressant; EGPA = eosinophilic granulomatosis with polyangiitis; NICE = National Institute for Health and Care Excellence; EMC = electronic medicines compendium; EULAR = European League Against Rheumatism; FDA = Food and Drug Administration; AEs = adverse events; CS = company submission; EAG = Evidence Assessment Group; CYC = cyclophosphamide; RTX = rituximab; UK = United Kingdom; PfC = points for clarification; CSR = clinical study report; BVAS = Birmingham vasculitis activity score; EULAR = European League Against Rheumatism; HRQoL = health-related quality of life; IP = investigational product; OLE = open-label extension; Q4W = once every 4 weeks; SAEs = serious adverse events; VDI = Vasculitis Damage Index.

3.2.1.1 Eligibility criteria

The eligibility criteria of the MANDARA trial included adult patients aged ≥ 18 years old who had a documented EGPA diagnosis, at least 6 months prior to screening; a stable OCS dose ≥ 7.5 mg/day prednisolone/prednisone (but not >50 mg/day) for at least four weeks; and a history of relapsing or refractory disease. The EAG agrees this aligns with the population in the NICE scope,¹⁴ which specifies adults with relapsing or refractory EGPA receiving OCS with or without stable IS therapy. However, patients with severe EGPA were excluded from the trial. As discussed in Section 2.1, clinical advice to the EAG confirmed benralizumab would be a relevant treatment for this subgroup of patients with severe disease, who are also more likely to receive treatment with cyclophosphamide and rituximab in UK clinical practice. The EAG note that prohibited medications in the MANDARA trial included cyclophosphamide and rituximab, which are also listed in the NICE scope. A key concern therefore arises over the representation of patients with severe EGPA, who may be receiving treatment with cyclophosphamide or rituximab. The Company reiterated the positioning of benralizumab for patients with non-severe EGPA during the FAC.¹⁷ Furthermore, the enrollment of patients with ANCA positive status was capped at 10% in the MANDARA trial.¹ Such patients were verified by clinical expert advice to the EAG, to present with more vasculitis manifestations, whilst patients with a more atopic phenotype that comprised the majority of the MANDARA study population would be less likely to receive treatment with cyclophosphamide or rituximab in UK practice. This is further discussed in Section 3.3.1.2. In response to the PfC (Question A9),¹⁶ the company provided further rationale for excluding patients with severe disease in the trial in addition to positioning of benralizumab in the treatment pathway. At the time of planning, MANDARA was designed to be a head-to-head, non-inferiority study to mepolizumab which was anticipated to be the SoC for when benralizumab would be entering clinical practice and evaluated by HTA bodies. Consequently, the study population of MANDARA was aligned as closely as possible to MIRRA, which also excluded patients with severe disease (further discussed in Section 3.2.2). The EAG agrees that the alignment of eligibility criteria between trials to be an appropriate approach at the time of designing the trial and this supports transitivity in the ITC included in the submission. Whilst post-hoc analysis from MANDARA which pooled data from both treatment groups, indicated adjusted rates of remission were

similar regardless of history of severe disease.²³, this still provides a key issue surrounding the uncertainty of clinical effectiveness and safety of benralizumab in patients with severe EGPA.

[REDACTED]

3.2.1.2 Baseline characteristics

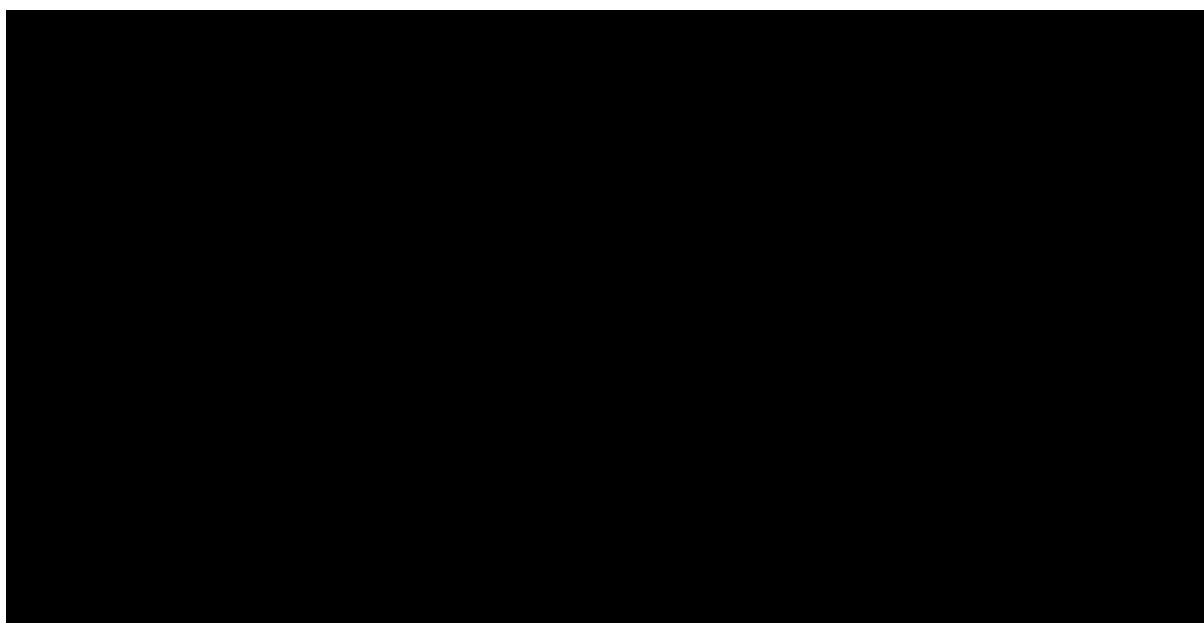
In the MANDARA trial ~13% (n=18) of 140 randomised patients were from four sites across the UK; [REDACTED] patients were randomised to the benralizumab treatment arm, and the remaining [REDACTED] patients to mepolizumab.⁵⁷ The demographic and disease characteristics were balanced between treatment arms, however, the data reported were not stratified by country. Clinical advice to the EAG confirmed the heterogeneity of the disease to vary greatly, and consultation with UK clinical experts by the company also indicated management of EGPA to vary depending on geographic location.⁹ Considering the relatively low proportion of patients from the UK enrolled in the MANDARA trial, the EAG had concerns around how well the patient population and SoC provided in the MANDARA trial reflected the UK patient population and clinical practice. The company in response to the PfC (Questions A4 and A5)¹⁶ provided OCS and IS usage by country and UK study site (Table 3.4 and Figure). The IS usage, and average OCS dose at baseline for the UK study population, were shown to comparable to the total study population. Furthermore, the progressive decline of OCS dosage throughout the 52-week double-blind period was also similar across countries. While differing prescribing practices across treatment sites may account for some of the observed variation, the EAG agree the small sample sizes across sites (London: n=[REDACTED]; Cambridge: n=[REDACTED]; Leicestershire: n=[REDACTED]; Portsmouth: n=[REDACTED]) prevent any inferences from being made.¹⁶

Table 3.4: OCS dosage and proportion of IS use by country, UK site, and overall study population from the MANDARA trial

	Baseline average daily OCS dose (mg)	Baseline proportion of patients on IS (%)
Total study population (N=140)	11.02	[REDACTED]
Belgium (N=[REDACTED])	[REDACTED]	[REDACTED]
Canada (N=[REDACTED])	[REDACTED]	[REDACTED]
France (N=[REDACTED])	[REDACTED]	[REDACTED]
Germany (N=[REDACTED])	[REDACTED]	[REDACTED]
Israel (N=[REDACTED])	[REDACTED]	[REDACTED]
Italy (N=[REDACTED])	[REDACTED]	[REDACTED]
Japan (N=[REDACTED])	[REDACTED]	[REDACTED]

USA (N=■)	■	■
UK (N=■)	■	■
London (N=■)	■	■
Cambridge (N=■)	■	■
Leicestershire (N=■)	■	■
Portsmouth (N=■)	■	■
Source: Response to PFCs, ¹⁶ Wechsler et al., 2024 ¹ Abbreviations: IS = immunosuppressant; OCS = oral corticosteroid. Footnote: OCS is administered as prednisolone		

Figure 3.1: OCS usage by country across the 52-week trial period (full MANDARA population)



Source: Response to PFCs,¹⁶ Wechsler et al., 2024¹
Abbreviations: OCS = oral corticosteroids.

Baseline characteristics of patients and treatment in the MANDARA trial, were confirmed in clinical expert interviews conducted by the company to be generalizable to patients and real-world practice in the UK.⁹ Clinical advice to the EAG verified baseline characteristics reflected patients with non-severe EPGA seen in UK clinical practice, but did not represent patients with severe disease. As discussed in Section 3.2.1.1, clinical advice to the EAG confirmed patients with severe EGPA were more likely to also be receiving treatment with cyclophosphamide or rituximab. Additionally, patients with severe EGPA in UK clinical practice, were typically older than the trial population; only ■ patients included in the MANDARA trial were >65 years of age.⁵ This reinstates the key issue over the efficacy of benralizumab in patients with severe disease in the UK, who also typically tend to be older.

3.2.2 MIRRA trial

Data on mepolizumab (from the MIRRA trial) were used by the company to form a connected network with benralizumab (from the MANDARA trial, NCT02020889)³⁷ to conduct Bucher ITCs and anchored MAICs (see Section 3.3 for further details).

The MIRRA trial (GlaxoSmithKline) is an international, multicentre phase III, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab for EGPA in subjects receiving standard of care therapy (defined as OCS with or without IS). Mepolizumab was administered as multiple subcutaneous injections (comprising three doses of 100 mg) every four weeks (13 administrations).² The trial was conducted in 31 academic centres and hospitals across nine countries including Belgium, Canada, France, Germany, Italy, Japan, Spain, USA and the UK. A summary of the EAG's critique of the design, conduct and analysis of MIRRA is presented in Table 3.5.

Table 3.5: Summary of EAG's critique on the design, conduct and analysis of the MIRRA trial

Trial design or conduct concept	Section in CS (and other sources) where methods are reported	EAG's assessment
Treatment	Table 12, Section D.1.6, ¹⁵ Wechsler et al., 2017 ²	Appropriate The intervention comprised three separate 100 mg mepolizumab doses administered as injections once every four weeks alongside standard of care. This matches the dosage and administration for EGPA provided by the FDA and EMC. ^{33,53} The trial had a follow-up period of 52 weeks. Long-term effectiveness of mepolizumab is documented in the long-term access programme. ^{60,61} The EAG are satisfied that the treatment dosage matches that recommended by regulatory authorities, and that the dosage of mepolizumab in the MIRRA trial is the same as that used in the MANDARA trial. ⁵
Randomisation	Wechsler et al., 2017 ² , GSK MIRRA protocol ⁶²	Appropriate Randomisation was performed with the use of a centralised computer-generated permuted-block schedule, stratified by (i) participation in a mechanistic-biomarker substudy in the United States; (ii) recruitment in Japan; and (iii) the remainder of the recruited participants. ² This is an apparent protocol deviation as two different ways to stratify the data were reported in the protocol. ⁶² Overall however,

		the EAG are satisfied that randomisation was performed adequately.
Allocation concealment	Wechsler et al., 2017 ² , GSK MIRRA protocol ⁶²	Appropriate As detailed above, randomisation was performed with the use of a centralised computer-generated block schedule. ² The overall process is appropriate, although the block-size is not reported. If the block size was small, it might be possible for sites to predict their allocation sequence, ⁶³ leading potentially to selection bias.
Eligibility criteria	Table 12, Section D.1.6 ¹⁵	Key issue 1 The trial assessed 151 patients for eligibility, of which 136 underwent randomisation. The MANDARA trial followed the inclusion criteria of MIRRA as discussed in Section 3.2.1.1. As discussed above, most notably, severe EGPA was excluded. This limits the direct applicability of the trial to patients with non-severe disease, which does not fully represent the patients reported in the NICE scope. Further detail is provided in Section 3.2.2.1.
Blinding	Wechsler et al., 2017 ²	Appropriate Masking encompassed participants and investigators. The mepolizumab and placebo preparations were identical in appearance and were administered in a blinded fashion. It is probable that blinding of outcome assessors was undertaken. Overall, the EAG are satisfied that all reasonable steps were employed to prevent knowledge of the intervention assignment influencing the effectiveness and adherence to the intervention and assessment of outcomes.
Baseline characteristics	Table 14, Section D.1.6 ¹⁵	Some concerns Clinical advice to the EAG has confirmed that the demographic and baseline disease characteristics of MANDARA were broadly representative of that seen in UK clinical practice. However, owing to the exclusion of severe EGPA in the trial, the EGPA population in the UK is likely to include severe disease which is not presented by the patients in MIRRA at baseline (see Key Issue 1, and Section 3.2.2.2 below).
Dropout rate	Wechsler et al., 2017 ²	Appropriate From the 136 patients who underwent randomisation, nine patients discontinued in the placebo arm. Amongst those patients who received mepolizumab, five discontinued treatment. The dropout rates

		were broadly comparable across treatment arms and ultimately 65 and 61 patients completed follow-up in the mepolizumab and placebo arms respectively. The EAG are satisfied that dropout was comparable between treatment arms, was not excessive and reasons for attrition were reported.
Statistical analyses	Wechsler et al., 2017 ²	Appropriate The trial was powered to detect a significant between-group difference of 29 percentage points in the percentage of participants who had remission for at least 24 weeks. The power calculation was based on a test for proportions, assuming that 25% of participants in the placebo group would achieve at least 24 weeks of remission, compared to 54% in the mepolizumab arm (corresponding to an OR of 3.5). To control for type I error, both primary endpoints needed to show positive results for the trial to be deemed successful. Efficacy end points were assessed in the intention-to-treat population. Safety end-points were analysed according to the actual regimen received. The EAG are satisfied that the statistical analysis was appropriate, and the relevant datasets were used to determine effectiveness.
Outcome measures	Table 15, Section D.1.6, ¹⁵ Wechsler et al., 2017 ²	Appropriate The NICE scope includes a wide variety of outcomes.¹⁴ The MIRRA trial encompassed two remission-based primary outcomes and a further 23 secondary outcomes.³⁷ HRQoL was not captured as an outcome in the MIRRA trial. Overall the EAG considers the outcomes to be appropriate, and the most important outcomes were assessed and subsequently used for cost effectiveness analysis.
Results: Efficacy outcomes	Table 2, Wechsler et al., 2017 ²	Appropriate Treatment with mepolizumab resulted in significantly more weeks of remission compared to placebo (28% of participants achieving ≥ 24 weeks of accrued remission versus 3% in the placebo group) (OR: 5.91; 95% CI: 2.68 to 13.03; $P < 0.001$). A higher percentage of participants in the mepolizumab group were in remission at both weeks 36 and 48 (32 versus 3%; OR: 16.74; 95% CI: 3.61 to 77.56). Remission was not achieved by 47% of participants in the mepolizumab group compared to 81%

		in the placebo group. The annualised relapse rate (ARR) was lower in the mepolizumab group (1.14) than in the placebo group (2.27), with a rate ratio of 0.50 (95% CI: 0.36–0.70; P<0.001). Furthermore, 44% of participants in the mepolizumab group maintained an average daily dose of prednisolone or prednisone of 4.0 mg or less during weeks 48 to 52, compared to 7% in the placebo group (OR: 0.20; 95% CI: 0.09 to 0.41; P<0.001).² The results demonstrate that treatment with mepolizumab resulted in more weeks in remission and a higher proportion of patients in remission than the placebo, resulting in reduced OCS use. The EAG agree that treatment with mepolizumab demonstrated clear clinical benefits to EGPA patients. See Section 3.3.1.4 detailing how the results of the placebo arm were used in the submission.
Results: Adverse events	Table 3, Wechsler et al., 2017 ²	Appropriate Safety was assessed on 68 patients in each of the mepolizumab and placebo arms. There was no significant difference in the percentage of patients who had an AE (97% versus 94%), however SAEs were higher for those in the placebo arm (26%) compared to treatment with mepolizumab (18%), possibly attributable to disease activity. The most commonly reported AEs were headache, nasopharyngitis, arthralgia, sinusitis and upper respiratory tract infection.² Whilst the full safety data are not available for the MIRRA trial, the results presented in Wechsler et al., 2017² show an acceptable safety profile.
Results: Subgroup analyses	Table S4 (supplementary appendix) ¹	Appropriate No subgroup analysis was specified in the NICE scope.¹⁴ Pre-specified sub-group analysis detailed the proportion of patients who achieved remission at both weeks 36 and 48.¹ Whilst most confidence intervals overlap, there appears to be a difference in the accrued duration of remission between patients with lower baseline blood eosinophil counts and lower baseline VDI score.¹ There is tentative evidence²⁵ that patients with severe asthma had the greatest effect of benralizumab treatment (see Section 2.1). Whilst this is potentially important, further evidence, from real-world evidence sources are needed to determine

		any differential effects based on baseline characteristics.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; EMC = electronic medicines compendium; FDA = Food and Drug Administration; NICE= National Institute for Health and Care Excellence; HRQoL = health related quality of life; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; ARR = annualised relapse rate; OCS = oral corticosteroid; AE = adverse event; SAE = serious adverse event; VDI = vasculitis damage index; OR = odds ratio; CI = confidence interval.		

Table 3.5: Summary of EAG's critique on the design, conduct and analysis of the MIRRA trial

Trial design or conduct concept	Section in CS (and other sources) where methods are reported	EAG's assessment
Treatment	Table 12, Section D.1.6, ¹⁵ Wechsler et al., 2017 ²	Appropriate The intervention comprised three separate 100 mg mepolizumab doses administered as injections once every four weeks alongside standard of care. This matches the dosage and administration for EGPA provided by the FDA and EMC. ^{33,53} The trial had a follow-up period of 52 weeks. Long-term effectiveness of mepolizumab is documented in the long-term access programme. ^{60,61} The EAG are satisfied that the treatment dosage matches that recommended by regulatory authorities, and that the dosage of mepolizumab in the MIRRA trial is the same as that used in the MANDARA trial. ⁵
Randomisation	Wechsler et al., 2017 ² , GSK MIRRA protocol ⁶²	Appropriate Randomisation was performed with the use of a centralised computer-generated permuted-block schedule, stratified by (i) participation in a mechanistic-biomarker substudy in the United States; (ii) recruitment in Japan; and (iii) the remainder of the recruited participants. ² This is an apparent protocol deviation as two different ways to stratify the data were

		reported in the protocol. ⁶² Overall however, the EAG are satisfied that randomisation was performed adequately.
Allocation concealment	Wechsler et al., 2017 ² , GSK MIRRA protocol ⁶²	Appropriate As detailed above, randomisation was performed with the use of a centralised computer-generated block schedule. ² The overall process is appropriate, although the block-size is not reported. If the block size was small, it might be possible for sites to predict their allocation sequence, ⁶³ leading potentially to selection bias.
Eligibility criteria	Table 12, Section D.1.6 ¹⁵	Key issue 1 The trial assessed 151 patients for eligibility, of which 136 underwent randomisation. The MANDARA trial followed the inclusion criteria of MIRRA as discussed in Section 3.2.1.1. As discussed above, most notably, severe EGPA was excluded. This limits the direct applicability of the trial to patients with non-severe disease, which does not fully represent the patients reported in the NICE scope. Further detail is provided in Section 3.2.2.1.
Blinding	Wechsler et al., 2017 ²	Appropriate Masking encompassed participants and investigators. The mepolizumab and placebo preparations were identical in appearance and were administered in a blinded fashion. It is probable that blinding of outcome assessors was undertaken. Overall, the EAG are satisfied that all reasonable steps were employed to prevent knowledge of the intervention assignment influencing the effectiveness and adherence to the intervention and assessment of outcomes.
Baseline characteristics	Table 14, Section D.1.6 ¹⁵	Some concerns Clinical advice to the EAG has confirmed that the demographic and baseline disease characteristics of MANDARA were broadly representative of that seen in UK clinical practice. However, owing to the exclusion of severe EGPA in the trial, the EGPA population in the UK is likely to include severe disease which is not presented by the patients in MIRRA at baseline (see Key Issue 1, and Section 3.2.2.2 below).
Dropout rate	Wechsler et al., 2017 ²	Appropriate From the 136 patients who underwent randomisation, nine patients discontinued in the placebo arm. Amongst those patients who received mepolizumab, five

		discontinued treatment. The dropout rates were broadly comparable across treatment arms and ultimately 65 and 61 patients completed follow-up in the mepolizumab and placebo arms respectively. The EAG are satisfied that dropout was comparable between treatment arms, was not excessive and reasons for attrition were reported.
Statistical analyses	Wechsler et al., 2017 ²	Appropriate The trial was powered to detect a significant between-group difference of 29 percentage points in the percentage of participants who had remission for at least 24 weeks. The power calculation was based on a test for proportions, assuming that 25% of participants in the placebo group would achieve at least 24 weeks of remission, compared to 54% in the mepolizumab arm (corresponding to an OR of 3.5). To control for type I error, both primary endpoints needed to show positive results for the trial to be deemed successful. Efficacy end points were assessed in the intention-to-treat population. Safety end-points were analysed according to the actual regimen received. The EAG are satisfied that the statistical analysis was appropriate, and the relevant datasets were used to determine effectiveness.
Outcome measures	Table 15, Section D.1.6, ¹⁵ Wechsler et al., 2017 ²	Appropriate The NICE scope includes a wide variety of outcomes.¹⁴ The MIRRA trial encompassed two remission-based primary outcomes and a further 23 secondary outcomes.³⁷ HRQoL was not captured as an outcome in the MIRRA trial. Overall the EAG considers the outcomes to be appropriate, and the most important outcomes were assessed and subsequently used for cost effectiveness analysis.
Results: Efficacy outcomes	Table 2, Wechsler et al., 2017 ²	Appropriate Treatment with mepolizumab resulted in significantly more weeks of remission compared to placebo (28% of participants achieving ≥ 24 weeks of accrued remission versus 3% in the placebo group) (OR: 5.91; 95% CI: 2.68 to 13.03; $P < 0.001$). A higher percentage of participants in the mepolizumab group were in remission at both weeks 36 and 48 (32 versus 3%; OR: 16.74; 95% CI: 3.61 to 77.56). Remission was not achieved by 47% of participants in

		the mepolizumab group compared to 81% in the placebo group. The annualised relapse rate (ARR) was lower in the mepolizumab group (1.14) than in the placebo group (2.27), with a rate ratio of 0.50 (95% CI: 0.36–0.70; P<0.001). Furthermore, 44% of participants in the mepolizumab group maintained an average daily dose of prednisolone or prednisone of 4.0 mg or less during weeks 48 to 52, compared to 7% in the placebo group (OR: 0.20; 95% CI: 0.09 to 0.41; P<0.001).² The results demonstrate that treatment with mepolizumab resulted in more weeks in remission and a higher proportion of patients in remission than the placebo, resulting in reduced OCS use. The EAG agree that treatment with mepolizumab demonstrated clear clinical benefits to EGPA patients. See Section 3.3.1.4 detailing how the results of the placebo arm were used in the submission.
Results: Adverse events	Table 3, Wechsler et al., 2017 ²	Appropriate Safety was assessed on 68 patients in each of the mepolizumab and placebo arms. There was no significant difference in the percentage of patients who had an AE (97% versus 94%), however SAEs were higher for those in the placebo arm (26%) compared to treatment with mepolizumab (18%), possibly attributable to disease activity. The most commonly reported AEs were headache, nasopharyngitis, arthralgia, sinusitis and upper respiratory tract infection.² Whilst the full safety data are not available for the MIRRA trial, the results presented in Wechsler et al., 2017² show an acceptable safety profile.
Results: Subgroup analyses	Table S4 (supplementary appendix) ¹	Appropriate No subgroup analysis was specified in the NICE scope.¹⁴ Pre-specified sub-group analysis detailed the proportion of patients who achieved remission at both weeks 36 and 48.¹ Whilst most confidence intervals overlap, there appears to be a difference in the accrued duration of remission between patients with lower baseline blood eosinophil counts and lower baseline VDI score.¹ There is tentative evidence²⁵ that patients with severe asthma had the greatest effect of benralizumab treatment (see Section 2.1). Whilst this is potentially important, further evidence, from real-world

	evidence sources are needed to determine any differential effects based on baseline characteristics.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; EMC = electronic medicines compendium; FDA = Food and Drug Administration; NICE= National Institute for Health and Care Excellence; HRQoL = health related quality of life; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; ARR = annualised relapse rate; OCS = oral corticosteroid; AE = adverse event; SAE = serious adverse event; VDI = vasculitis damage index; OR = odds ratio; CI = confidence interval.	

3.2.2.1 Eligibility criteria

The MANDARA trial was conducted in 50 centres across nine countries.⁶⁴ Due to the rarity of the condition, it is conceivable that some of the patients who enrolled in MANDARA were previously included in the placebo arm of the MIRRA trial as there was an overlap in trial sites as well as countries.

Adult patients with a history of relapsing of refractory disease, taking a stable dose of OCS with or without a stable IS dose (excluding cyclophosphamide) were eligible for inclusion. Patients with life-threatening EGPA within three months prior to screening and through randomisation were excluded, as were patients with organ-threatening EGPA.^{5,62} Full reporting of the inclusion criteria of MIRRA, alongside MANDARA are described in Section D.1.6 in the CS.⁵ The inclusion criteria across the trials are very comparable. As detailed in the response to clarification question A9,¹⁶ MANDARA was designed to be a head-to-head, non-inferiority study to mepolizumab (which was anticipated to be the standard of care for when benralizumab was being evaluated by regulatory authorities).

As with the MANDARA trial, the population was restricted to cases of non-severe EGPA. The EAG notes that this is not in line with the original NICE scope for this appraisal¹⁴ and therefore the EAG considers this a key issue (see Table 1.2). The populations in both trials exclude patients with severe EGPA, and clinical advice to the EAG has confirmed that benralizumab is likely to be efficacious to patients with severe disease. Indeed, in MIRRA which assessed the efficacy of an mepolizumab, which like benralizumab is an anti-IL5 monoclonal antibody, there was tentative evidence of a stronger effect relative to placebo in non-severe patients with indicators of greater disease severity (baseline blood eosinophil count ≥ 150 cells/ μ L and baseline VDI score ≥ 5 (Table 3.6)).¹ There was a significant difference ($p < 0.05$) for patients with a baseline blood eosinophil count ≥ 150 cells/ μ L (OR 95% CI: 26.10 (7.02 to 97.02)) compared to those with counts < 150 cells/ μ L (OR 95% CI: 0.95 (0.28, 3.24)) for mepolizumab/placebo. This pattern is replicated in the baseline VDI scores, although the difference is not statistically significant. Whilst the small sample sizes increase uncertainty, mepolizumab may show greater efficacy in the patients with more severe symptoms amongst patients with non-severe disease. As benralizumab was shown to be non-inferior to mepolizumab in the MANDARA trial, a similar pattern might be replicated for benralizumab. Indeed, in the CALIMA trial which looked at benralizumab as an add-on treatment for patients with severe, uncontrolled, eosinophilic asthma, the study authors found that patients who had experienced three or more exacerbations in the previous year (i.e., greater asthma severity at baseline) had the greatest effects of benralizumab treatment.²⁵

demographic and baseline disease characteristics of MANDARA were broadly representative of that seen in UK clinical practice. Since there is comparability in summary data between MANDARA and MIRRA it is likely that this is also the case for MIRRA. As such, the baseline characteristics of MIRRA by association are broadly representative of that seen in UK clinical practice.

As discussed above (Section 3.2.2.1), MIRRA excluded patients with severe EGPA in the trial. Consequently, the EGPA population in the UK is likely to include severe disease which is not presented by patients in MIRRA at baseline (see Key Issue 1).

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

The final scope issued by NICE,¹⁴ defined the relevant comparator as established clinical management without benralizumab, including OCS, CYC, other IS agents, and RTX. In the CS Section B.1.1 (Table 1),⁵ the company after consulting clinical guidelines, clinical expert opinion, and UK prescription data determined that OCS with or without IS formed SoC in the UK. The MANDARA trial, the only trial providing relevant clinical data on the intervention in line with the decision problem, compared the efficacy and safety of benralizumab versus mepolizumab in patients with EGPA. As mepolizumab treatment is not a relevant comparator, nor a NICE recommended treatment option in the UK, the company performed an ITC to generate efficacy estimates of benralizumab versus OCS with or without IS, in participants with EGPA. Additionally, the company performed an anchored MAIC to validate the results of the ITC. The EAG's critique regarding the methodology of the ITC and MAIC are presented in the Sections 3.3.1 and 3.3.2.

3.3.1 Bucher ITC

The company first carried out a feasibility assessment to identify relevant clinical studies that would permit an anchored ITC with the MANDARA trial (detailed in CS Section B.2.9).⁵ With mepolizumab as the common comparator, MIRRA and MANDARA were concluded to permit the generation of comparative efficacy estimates of benralizumab versus SoC. Differences in trial design, population and outcome measurements were reasoned to not be clinically meaningful, and a Bucher ITC was deemed appropriate. Table 3.7 presents a summary of the EAG's comments regarding the methodology of the Bucher ITC with key points expanded upon in the following sections.

Table 3.7: Summary of EAG's critique of the Bucher ITC methods

Aspect of Bucher ITC design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	B.2.9, p.52-55 ⁵	Appropriate The company performed ITCs using Bucher's method.⁶⁵ which assumes there are no important differences between trials in the distribution of effect-modifying variables. Considering the heterogeneity of EGPA, and the limited number of relevant trials, application of a Bucher ITC may lead to unreliable estimates. However, the company in consultation with clinical experts

		concluded apparent baseline differences between trials to not be clinically meaningful, and an anchored MAIC was performed to account for uncertainties in the ITC. The EAG are satisfied with the company's statistical approach to the ITC.
Included and excluded studies	Appendix D, Section D.1.5, p.33-36 ¹⁵	Some concerns The company conducted a feasibility assessment for generating an ITC between benralizumab and SoC for EGPA. The company characterised SoC in the UK to differ from the NICE scope to encompass OCS with or without IS. Clinical advice to the EAG confirms treatment with RTX and CYC may form SoC for patients with severe EGPA but are unlikely for those with non-severe disease. See Section 3.3.1.1 below for further comment.
Included study characteristics and demographics	D.1.6 p45 ¹⁵	Key concern Patients from the UK only comprised ~13% of the MANDARA trial population.^{1,55} The EAG therefore questioned in the PfC (question A4 and A5)¹⁶ the treatment received by country and by UK study site. The EAG note that patients with severe EGPA were excluded from both the MANDARA and MIRRA trials, therefore there is substantial uncertainty as to the efficacy of benralizumab in patients presenting with severe disease included within the NICE scope. Additionally, there is some concern relating to a possible lack of independence of participants across the two trials. See Section 3.3.1.2 3.3.1.1 below for further comment.
Transitivity assumption	B.2.9.1, p.52-53; Appendix D Section D.1.6 p37-49; D.1.10, p.51 ^{5,15}	Some concerns Minor differences between MIRRA and MANDARA trials were identified by the company and were concluded not to be clinically meaningful in clinical expert interviews held by the company. The EAG consider there to be considerable similarities between the MANDARA and MIRRA trials, enabling an ITC to be conducted. However, there are some apparent differences in baseline disease severity which could potentially impact on effect estimates of benralizumab versus SoC but this is very uncertain. MIRRA was conducted 5 years prior to MANDARA and this may account for some variation, particularly regarding disease and treatment characteristics at baseline. See Section 3.3.1.3 3.3.1.3 below for further comment.
Results	B.2.9.2, p.54; Appendix D, Section D.1.9, p.50 ^{5,15}	Some concerns Comparative efficacy of benralizumab versus SoC was determined for nine outcomes which encompass remission, relapse and OCS dosage endpoints from the MANDARA and MIRRA trials. Compared to SoC treatment, benralizumab showed a statistically significant improvement in the proportion of participants in remission at both

		Weeks 36 and 48 (odds ratio: [REDACTED] (95% CI: [REDACTED], [REDACTED])) and reduced annualised relapse rate (rate ratio: [REDACTED] (95% CI: [REDACTED], [REDACTED])). For all other endpoints measured, results of the Bucher ITC were also in favour of benralizumab over SoC. Two outcomes were also assessed in an anchored MAIC and applied in the company's economic analysis. Some uncertainty remains over outcomes either not directly assessed in the ITC or not validated in the MAIC. See Section 3.3.1.4 below for further comment.
Sensitivity analyses	B.2.9.3, p.55; Appendix D, Section D.1.10 p50-54 ^{5,15}	Appropriate To address uncertainties in the Bucher ITC the company also performed an anchored MAIC with MANDARA and MIRRA. A summary of the EAG's critique of the MAIC is provided in Table 3.7.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OCS = oral corticosteroid; RCT = randomised control trial; SLR = systematic literature review; SoC = standard of care; IS = immunosuppressant; PfC = points for clarification; NICE = National Institute for Health and Care Excellence; CYC = cyclophosphamide; RTX = rituximab; UK = United Kingdom; OR = odds ratio; CI = confidence interval.		

3.3.1.1 Included and excluded studies

In the CS Section B.2.9.1, the company conducted a feasibility assessment which evaluated data availability, heterogeneity between trials and network connectivity, for generating an ITC between benralizumab and SoC for EGPA.⁵ MANDARA excluded patients with severe disease, or patients that had recently received previous cyclophosphamide or rituximab treatment,¹ subsequently the company reasoned cyclophosphamide and rituximab not to be appropriate comparators for this submission (see Section 2.2 for further discussion). The EAG agree OCS with or without IS matches SoC in the UK for patients presenting with non-severe EGPA, however, cyclophosphamide and rituximab form part of the treatment pathway for patients with severe disease. Uncertainty therefore remains in the clinical effectiveness of benralizumab in patients with EGPA compared to SoC for patients with severe disease, which can include treatment with cyclophosphamide or rituximab in the UK.

During the feasibility assessment for an ITC the company also concluded that although these trials included the evaluation of treatments with OCS with or without IS, only the MIRRA trial allowed for an anchored ITC with the MANDARA trial.⁵ The EAG note key differences in the study designs, baseline characteristics and outcomes of the other six RCTs in comparison to the MANDARA trial, which would preclude generation of a robust anchored ITC. With further consideration of the limited available evidence and rarity of EGPA, the EAG therefore agree the approach taken by the company to allow an anchored ITC based on patients with relapsing or refractory, non-severe EGPA to be performed appropriate.

3.3.1.2 Included study characteristics and demographics

Clinical advice to the EAG confirms EGPA presents as a heterogenous disease, which can affect multiple organs, and therefore requires a multidisciplinary approach to management of the disease. Furthermore, consultation with UK clinical experts by the company also highlighted management of EGPA to vary by geographic location.⁹ Both the MANDARA and MIRRA trials were conducted globally including study sites within the UK. However, only ~10%

(13/136) of the total study population in the MIRRA trial were based in the UK, while ~48% (65/136) patients were based in North America, and the remaining ~42% were based in Belgium (n=3), France (n=13), Germany (n=19), Italy (n=13), Spain (n=4) and Japan (n=6).² Similarly in the MANDARA trial ~13% (18/140) of patients were based in UK across a total of four sites.^{1,55,57} The remaining MANDARA study population were based in North America (32/140), Belgium (n=4), France (n=33), Germany (n=17), Italy (n=18), Israel (n=10), and Japan (n=8).¹ The relatively low proportion of UK based patients in both trials raised some concerns to the EAG as to the translatability of the two trials to the patient population, and clinical practice in the UK.

As discussed in Section 3.2.1.2 the OCS dosage and IS usage broken down by country and UK study site in the MANDARA trial were provided by the company in response to the PfC (Question A4 and A5).¹⁶ The company only have access to published summary-level data from the MIRRA trial, therefore country specific data from the MIRRA trial were not provided. The OCS dosage and IS therapy in the UK were comparable to the total study population. Across UK study sites, OCS dose and IS therapy varied, but the company reasoned no firm conclusions can be made owing to differing prescribing practices and small samples sizes.¹⁶ Patient baseline characteristics in MANDARA, and baseline treatment usage were confirmed in clinical expert interviews conducted by the company to be generalisable to patients and real-world practice in the UK.⁹ This has also been verified independently through clinical expert advice to the EAG. The EAG therefore consider the OCS dosage and IS usage presented in the MANDARA trial to be translatable to the UK patient population. However, there are concerns due to exclusion of patients with severe EGPA in both the MANDARA and MIRRA trials. Clinical expert advice to EAG confirmed patients in the MANDARA trials presented with non-severe EGPA and indicated benralizumab would also be a relevant treatment in clinical practice for patients with severe disease. Furthermore, clinical advice to the EAG is that patients with severe disease tend to be older; while only [REDACTED] patients included in the MANDARA trial were >65 years of age.⁵ The EAG believe that this raises a key issue of uncertainty of the efficacy of benralizumab in patients with severe disease in the UK, who typically tend to be the older.

[REDACTED]

3.3.1.3 *Transitivity assumption*

A key assumption of Bucher ITCs is an absence of important differences between trials in the distribution of effect-modifying variables.⁶⁵ While the EAG agree there are considerable similarities between the MANDARA and MIRRA trials to enable an ITC to be conducted, there are some differences which may have a confounding impact on effect estimates; these are expanded on in the following section.

In the CS, the company stated the two trial designs were comparable with some minimal differences (CS Section D.1.6, Table 12).¹⁵ Firstly MIRRA used a placebo-controlled design, while MANDARA had an active-comparator non-inferiority design. Both trials were phase III, included the common comparator mepolizumab, and enrolled a similar number of patients. Furthermore, as described in Section 3.3.1.2, study locations were overall similar; both trials included a comparable number of patients from the UK (~10-[REDACTED]).^{1,2,5} Of note, MIRRA also

enrolled patients in Spain, and MANDARA also enrolled patients in Israel and there was a markedly higher proportion of patients from North America in MIRRA than the MANDARA trial (~48% vs ~[REDACTED]).^{1,2}

Both trials exclusively enrolled patients diagnosed with relapsing or refractory EGPA and were matched according to the eligibility criteria. Only minimal differences in patient eligibility criteria are notable, which were highlighted by the company (CS Section D.1.6, Table 13)¹⁵: allergy, intolerance, contradictions, other concurrent medical conditions, prohibited medications, parasitic infection and hepatitis status. Furthermore, comparison of the seven pre-determined efficacy outcomes and their definitions from MANDARA and MIRRA (CS Section D.1.6, Table 15)¹⁵, identified only one outcome definition to present minor differences: the average daily OCS dose during the last 4 weeks of the study (Week 48–Week 52). The EAG agree the definition for MANDARA trial to be more conservative; however, they do not believe that the difference in definitions, nor the eligibility criteria or trial designs to constitute a substantive difference between the trials. Similarity between MANDARA and MIRRA patient baseline characteristics was also reported on in the CS (CS Section D.1.6, Table 14).¹⁵ The EAG note that the three UK clinical experts interviewed by the company all agreed that the study designs and eligibility criteria of the two trials were comparable.⁹ However, compared to MANDARA, two of the clinical experts highlighted the trial population of MIRRA at baseline presented with higher BVAS, indicative of higher disease severity, and all three noted treatment with OCS/IS in MIRRA was greater. Fewer treatment options at the time of the MIRRA trial, 5 years prior to MANDARA, was provided as justification for the observable differences; the level of disease severity may have been addressed with mepolizumab during or after the MIRRA trial thus reducing the levels of IS/OCS treatment. Furthermore, more clinical experience in eosinophil targeted treatment and recent guidelines aiming towards tapering of OCS, may have encouraged a downward trend in OCS treatment by physicians.¹

The difference in the timing of the two trials is also relevant; MIRRA took place prior to the coronavirus disease 2019 (COVID-19) pandemic (February 2014–September 2016),³⁷ while MANDARA took place before/during the pandemic (October 2019–August 2023). In the latter trial, COVID-19 was the most common adverse event, experienced by 21% (15/70) and 27% (19/70) of patients in the benralizumab and mepolizumab groups respectively.¹ The MANDARA CSR states that [REDACTED]

[REDACTED]

[REDACTED] The effect of social distancing measures during the pandemic was suggested in the main study publication as another potential reason for the lower percentage of patients who had a relapse in MANDARA compared to those in MIRRA.¹

In the CS Section D.1.10, the company presented a list of potential treatment effect modifiers including eligibility criteria and baseline characteristics from the MANDARA and MIRRA trials to four clinicians.¹⁵ Differences in the ranked, potential effect modifiers were noted between study populations by the clinicians, however these differences were not considered to be meaningful, and confirmed similarity in the trial design, population, and outcomes measurements between the two trials.⁵ The company also conducted an anchored MAIC which was adjusted based on a pooled clinical expert-ranked-ordered list of potential, treatment-effect modifiers (see Section 3.3.2 for further discussion).¹⁵ Overall, the EAG consider this approach provides support for the unadjusted Bucher ITC, however as discussed

later in Section 3.3.1.4, not all outcomes in the ITC were validated in the MAIC leaving some uncertainty.

3.3.1.4 Results

The company presented the comparative efficacy of benralizumab versus SoC for nine outcomes in the Bucher ITC, related to remission, relapse and OCS dosage. As discussed in Section 2.3, the definitions of these three outcomes incorporate additional outcomes included in the NICE scope, such as IS usage. Therefore, the clinical effectiveness cannot be independently derived for all outcomes in the ITC. Furthermore, limitations of SF-36 used to measure HRQoL in MANDARA were highlighted by the company which led to the undertaking of two studies to generate more robust evidence to accurately represent QoL in an EGPA-specific population for implementation in the cost-effectiveness analysis (for further discussion see Section 4.2.6).

The following two outcomes from the ITC: proportion of participants in remission and annualised relapse rate were applied in the company's economic analysis and are presented in Table 3.8. Compared to SoC, the odds of patients being in remission (main remission definition) at both Week 36 and Week 48 was estimated to be [REDACTED] times higher for those receiving benralizumab.⁵ Additionally, treatment with benralizumab was estimated to have a [REDACTED] lower risk of relapse over the course of the year compared to SoC.⁵ The company's consultation with UK clinical experts found that the ITC results were viewed as reasonable.⁹ To further validate the results, the company conducted an anchored MAIC for the two outcomes which inform the model, which was adjusted based on the pooled clinical expert rank-ordered list of potential treatment-effect modifiers (discussed in Section 3.3.2.13.3.1.3). The company in response to the PfC (Question A14)¹⁶ confirmed the inputs for the ITC and MAIC to the EAG.⁵ The EAG agree the MAIC results for the two outcomes corroborated those generated from the ITC, providing credibility to the Bucher ITC (Table 3.9). However, after adjustment in the MAIC, the effective sample size of the MANDARA trial reduced from 140 to 55,¹⁵ raising some concern; this is further discussed in Section 3.3.2.13.3.2. The EAG further note that Bucher ITCs were conducted for the remaining seven outcomes (CS Section D.1.9, Table 16),¹⁵ however, MAICs were not, leaving some uncertainty relating to these seven outcomes. Considering these additional outcomes did not inform the model, the EAG do not believe this approach to be a major concern.

Table 3.8: Bucher ITC and MAIC results

Outcome	Bucher ITC	MAIC
Binary endpoint	OR (95% CI)	OR (95% CI)
Proportion of patients in remission at both Week 36 and Week 48 (main remission definition)	[REDACTED]	[REDACTED]
Rate endpoint	RR (95% CI)	RR (95% CI)
Annualised relapse rate	[REDACTED]	[REDACTED]
Source: CS section B.2.9.2 Table 19; ⁵ Appendix D, D.1.9 Table 19 ¹⁵ Abbreviations: CI = confidence interval; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OR = odds ratio; RR = rate ratio.		

3.3.2 Matching-adjusted indirect comparison

To support this submission and validate the Bucher ITC results the company performed an anchored MAIC (CS Section B.2.9.3 and D.1.10).^{5,15} Potential effect modifiers identified from the literature and across both MIRRA and MANDARA trials were compiled. After consultation with clinical experts on how likely the covariates were to modify treatment effect, the MAIC was adjusted based on a resulting pooled rank-ordered list of factors. Table 3.9 presents a summary of the EAG's comments regarding the methodology of the anchored MAIC with key points expanded upon in the following section.

Table 3.9: Summary of the EAG's critique of the MAIC methods

Aspect of MAIC design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	Appendix D, Section D.1.10, p.50-53 ¹⁵	Appropriate A MAIC was conducted using data from MANDARA and MIRRA trials to validate the Bucher ITC. A pooled rank-ordered list of potential treatment effect modifiers was applied to adjust the MANDARA trial population to that of summary-level data from the ITT population of MIRRA. To estimate the difference in efficacy between benralizumab and placebo for two outcomes (main remission and annualised remission rates) from the adjusted MANDARA population and MIRRA trial, negative binomial distributions with logit link function were used.
Covariates included in the MAIC	Appendix D, Section D.1.10, p.51-53 ¹⁵	Some concerns The MAIC adjusted for 11 factors considered to be important by four clinical experts based in the UK, USA and Canada.¹⁶ After patients with missing baseline characteristics were removed and adjustment, the effective sample size was reduced to 55 (from 140 in the FAS) for the MANDARA trial population. The analyses used summary-level data from the MIRRA trial ITT population,² while individual patient data from the MANDARA trial were based on the FAS, which the company had full access to. See Section 3.3.2.13.3.2 below for further comment.
Results	Appendix D, Section D.1.10, p.54 ¹⁵	Appropriate The MAIC demonstrated favourable treatment effects for benralizumab compared to SoC for main remission (OR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]) and annualised relapse rate (RR: [REDACTED]; 95% CI: [REDACTED], [REDACTED]) similar to that found in the Bucher ITC results.
Abbreviations: CS= company submission; EAG= Evidence Assessment Group; FAS= full analysis set; ITC= indirect treatment comparison; ITT= intention to treat; MAIC= matching-adjusted indirect comparison; SoC= standard of care; OR= odds ratio; RR= rate ratio; CI= confidence interval; UK = United Kingdom; USA = United State of America.		

3.3.2.1 Covariates included in the MAIC

In the CS Section D.1.10, the company presented a list of potential treatment effect modifiers including eligibility criteria and baseline characteristics from the MANDARA and MIRRA trials and drawn from consulting the literature.¹⁵ Four clinical experts were individually consulted to identify “crucial” factors, and to rank the remaining “not important” factors in order of importance based on the likelihood the covariate to modify treatment effect (Table 3.10). In response to the PfC (Question A6)¹⁶ the company confirmed these clinical experts to be global specialists in the management and research of EGPA; one UK-based expert in vasculitis, lupus and rare renal disease; two US-based experts specializing in asthma, vasculitis, eosinophilic lung disease and EGPA; and one Canadian-based expert with a special interest in vasculitis.

A resulting pooled rank-ordered list of potential treatment effect modifiers was used to adjust the MANDARA trial population to match outcome definitions and the distribution of potential treatment effect modifiers in the MIRRA trial. The top 11 factors considered most important and adjusted for in the MAIC; in descending order were: prednisolone or prednisone dose, refractory disease, absolute eosinophil count per mm³ at baseline, immunosuppressive therapy [at baseline], relapsing disease, sinonasal abnormality, immunosuppressive therapy [historical], body mass index, duration since diagnosis of EGPA, BVAS>0 at baseline, and ANCA-positive status [historical].¹⁵ After reweighting the remaining participants, the means, and standard deviations of covariates from the MANDARA trial were almost equal to those of the published MIRRA trial, which is used as the reference (CS Section D.1.10).¹⁵ After adjustment the effective sample size was reduced to 55 (from 140 in the full analysis set) for the MANDARA trial population.¹⁵ As the company only have access to the published summary-level data from the MIRRA trial which the estimates were based on, the EAG have some concern over the reduced power and accuracy of the analyses. However, the EAG note that while the 95% confidence interval for the OR of remission widened, the confidence interval for the RR of the ARR, remained closely matched to that from the Bucher ITC (Table 3.8**Error! Reference source not found.**).

Table 3.10: Ranking of Potential Treatment Effect Modifiers

Characteristic	Clinician Advisor Ordering				Average of Clinical Advisors
	#1	#2	#3	#4	Overall
Prednisolone or prednisone dose (mg/day)	████	████	████	████	I
Refractory disease	████	████	████	I	I
Absolute eosinophil count per cubic mm (at baseline)	████	████	I	████	█
Immunosuppressive therapy at baseline	I	████	████	I	I
Relapsing disease	████	████	I	I	I
Sinonasal abnormality	I	████	████	I	I
Immunosuppressive therapy (historical)	I	████	█	I	I
BMI	I	████	█	I	I

Duration since diagnosis of EGPA	■	■	■	■	■
BVAS >0 at baseline	■	■	■	■	■
ANCA-positive status (historical)	■	■	■	■	■
Neuropathy	■	■	■	■	■
Nonfixed pulmonary infiltrates	■	■	■	■	■
Cardiomyopathy	■	■	■	■	■
Palpable purpura	■	■	■	■	■
Glomerulonephritis	■	■	■	■	■
Race	■	■	■	■	■
Alveolar haemorrhage	■	■	■	■	■
Age	■	■	■	■	■
Sex	■	■	■	■	■
Biopsy evidence	■	■	■	■	■
Source: CS Appendix D.1.10 (Table 17) ¹⁵ Abbreviations: ANCA = anti-neutrophil cytoplasmic anti-body; BMI = body mass index; BVAS = Birmingham Vasculitis Activity Score; EGPA = eosinophilic granulomatosis with polyangiitis; MG = milligram.					

3.4 Conclusions of the clinical effectiveness section

A SLR was conducted in June 2023 and updated in August 2024 to identify literature relevant to the NICE scope.¹⁴ The EAG identified minor concerns on the sensitivity of the search strategies and on the adoption of a prioritisation strategy, which excluded observational studies. While the EAG agree the latter enabled identification of the highest quality and most relevant evidence for inclusion in the ITC, observational studies may have provided supportive, real-world evidence to strengthen this submission. In total 12 studies were included in the SLR; however only the MANDARA trial matched the NICE scope, which investigated the efficacy and safety of benralizumab compared to mepolizumab in the induction of remission in patients with refractory or relapsing non-severe EGPA.¹

During MANDARA, which was an international, multicentre, phase III trial (NCT04157348), 140 patients were randomised to receive benralizumab or mepolizumab, with OCS, with or without IS, over a 52-week double-blind period.¹ The study met its primary endpoint with benralizumab treatment resulting in remission (BVAS = 0 and OCS dose ≤4 mg/day) of EGPA in 57.7% patients, which was non inferior to mepolizumab treatment (56.5%).^{1,5} Secondary endpoints, including ARR and reduction in OCS usage also supported noninferiority between treatment arms. Participants that completed the trial, could then enrol on to an OLE, which is still ongoing. Interim results at one year, supplied by the company in this submission, indicate durability of response to benralizumab treatment beyond the 52-week double blind period.⁴

In the absence of a head-to-head trial, the company assessed the eight RCTs identified in the SLR to ascertain relative efficacy estimates of benralizumab versus SoC. The company

concluded MIRRA was the only trial that would permit the generation of an anchored ITC with MANDARA. MIRRA, also an international, multicentre, double-blind, phase III trial, investigated the efficacy and safety of mepolizumab for refractory or relapsing non-severe EGPA, in patients receiving SoC therapy (defined as OCS with or without IS)(NCT02020889).² A Butcher ITC connected through the common comparator mepolizumab was performed using data from MANDARA and MIRRA.

The ITC demonstrated benralizumab treatment to provide substantial improvement in the proportion of patients in remission and reduction in annualised relapse rate, compared with SoC, which fed into the cost-effectiveness analysis. These two outcomes were further validated in a MAIC, which was adjusted using a pooled rank-ordered list of potential treatment effect modifiers. The EAG have some concern over the reduced power and accuracy of the latter analyses as the company only have access to the published summary-level data from MIRRA. Furthermore, the EAG raised some concerns over the outcomes used in the ITC and the transitivity of the two trials and also whether the participant populations in the two trials were wholly independent. Despite these concerns, the EAG are satisfied with the quality of the trials, and the way in which these have been synthesised to achieve a SoC comparison for benralizumab, particularly considering the availability of EGPA specific evidence.

Both MANDARA and MIRRA trial populations excluded patients with severe EGPA. This meant that the submission reflected only a proportion of the population identified in the NICE scope (adults with relapsing or refractory EGPA, receiving OCS with or without stable IS therapy) and was identified as a key issue by the EAG. The Company further reiterated the positioning of benralizumab for patients with non-severe EGPA in the FAC. Clinical advice to the EAG indicates that benralizumab would likely be used in clinical practice for patients with severe disease and noted a subset of these patients already receive benralizumab in the indication of severe eosinophilic asthma. Furthermore, a post-hoc analysis of MANDARA, which pooled patients from both treatment groups, indicated similar efficacy endpoints regardless of history of severe disease.²³

The narrower population in the CS is reflected in the company's selection of OCS with or without IS as the appropriate comparator for benralizumab in addition to OCS with or without IS. Clinical advice to the EAG confirms that while agents such as cyclophosphamide and rituximab have limited use in the non-severe population included in MANDARA, cyclophosphamide and to a lesser degree rituximab would be indicated in patients with more severe disease. The EAG are satisfied that OCS with or without IS is the appropriate comparator for the patients with non-severe disease included in the CS. However, the evidence presented has uncertain relevance to patients with severe disease, for whom cyclophosphamide and rituximab may be appropriate additional or alternative comparators.

In conclusion, other than the minor concerns and key issue outlined above, the EAG do not believe that these represent substantive issues with the reliability or relevance of the effectiveness evidence. Apart from these the EAG accept that the company's treatment of the evidence was broadly appropriate and is unlikely to have resulted in substantive issues in terms of the reliability and relevance of the evidence. They therefore consider that, given the rarity of the disease and the scarcity of the RCT evidence, the evidence is reliable with respect to the population to whom it is directly relevant: people with relapsing or refractory EGPA being treated with OCS with or without IS who do not have severe disease. This population is a subset, albeit a majority, of those defined in the scope.

4 COST EFFECTIVENESS

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

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search-related section also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

Table 4.1 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness.

Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Appendix G.1.1 pp. 69-72 (EEs and HCRU original and update searches and also HRQoL update). Appendix H.1.1 p. 118-120 (original HRQoL search)	Appropriate The sources are appropriate. The company could also have considered searching the CEA Registry at Tufts and the RePEc/IDEAS databases which can also be useful sources for economic evaluations (free versions of both are available). Please also see the source-related comments in Table 5.1.1 which are also relevant for these searches.
Search strategies	Appendix G. 1.1 pp. 73-109 (EE and HCRU original and update searches, also HRQoL update). Appendix H.1.1 pp. 120-144 for original HRQoL search. Appendix I.1.1 for HCRU conference proceedings, website, other sources search terms pp. 151-162.	Some concerns In two of the searches a 'combination line' did not include all relevant lines resulting in 'orphan lines'. This means that potentially relevant studies may have been missed by the searches. Please see section 4.1.1 below for further details. Please also see the search strategy-related comments in Table 3.1 which are also relevant for these searches.
Search filters	Appendix G. 1.1 pp. 72, 73-109 (EE and HCRU original and update searches,	Appropriate Appropriate search filters were applied.

	and HRQoL update). Appendix H.1.1 pp. 120-144 for original HRQoL search.	
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HCRU = healthcare resource use; EE = economic evaluations; SLR = systematic literature review; CEA = cost effectiveness analysis; RePEc = research papers in economics.		

4.1.1 Search methods for the cost effectiveness review

All searches were conducted in June 2023 and updated in August 2024 and so are considered up to date. The original searches covered both economic evaluations and healthcare related cost and resource use simultaneously (Appendices G and I)^{43,45} with a separate search for HRQoL (Appendix H).⁴⁴ The updated search covered all three simultaneously i.e. economic evaluations, healthcare resource use and cost and HRQoL. The critique for all three searches are presented in this section 4.1.1 Search methods for the cost effectiveness review and the search related comments in Table 3.1 are also relevant to these searches.

Search strategies

In two of the searches a 'combination line' did not include all relevant lines resulting in 'orphan lines'. In Table 23 (update MEDLINE search, Appendix G)⁴³ only the HRQoL terms are included in the search and the terms for economic evaluations are missing from the combination lines (lines 97 and 98). In effect, the MEDLINE searches for economic evaluations and healthcare resource use were not updated and so only covered up to June 2023. In Table 37 (original search in CENTRAL/CDSR, Appendix H)⁴⁴ in line 53 only part of the search filter for HRQoL was included in the search, lines 4 to 16 are missing. This means that only a partial search for HRQoL was conducted in CENTRAL/CDSR for the original SLR. Please also see the search strategy-related comments in Table 4.1 which are also relevant for these searches. These considerations led to some concerns as to whether potentially relevant studies may have been missed by the searches.

4.1.2 Conclusions of the cost effectiveness review

The data source for cost-effectiveness review and search filters used were considered appropriate for the review. But the EAG has some concerns over the precision and sensitivity toward retrieving economic evaluation studies. Although the rarity of EGPA population does justify the fact that there were no relevant studies identified in the review, to inform cost-effectiveness analysis, it is all the more reason for using a better refined search strategy in order to not miss any relevant studies.

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

NICE reference case checklist

Table 4.2 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis.

Table 4.2 : NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	Benralizumab as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) receiving oral corticosteroids (OCS) with or without stable immunosuppressive (IS) therapy	Key issue 1 The company excluded the patients with severe EGPA from the baseline population in their submission. This group of patients requires more toxic treatments. The EAG has some concerns regarding generalizability of the assessment to a patient population with high-level of severity.
Comparators	Established clinical management without benralizumab, including: • OCS (do not currently have a marketing authorisation in the UK for this indication) • CYC (does not currently have a marketing authorisation in the UK for this indication) • Other IS agents (do not currently have a marketing authorisation in the UK for this indication) • RTX (does not currently have a marketing authorisation in the UK for this indication)	Key issue 1 Due to limiting treatment to the non-severe patient population, CYC and RTX comparators were excluded. The company indicated that, according to clinical guidelines and expert opinions, these treatments are appropriate for severe cases of EGPA, which they did not address in this submission. Appropriate For the non-severe patient population, the chosen comparator (SoC with OCS and IS) was appropriate.
Perspective on outcomes	• Mortality • Remission rates • Total accrued duration of remission • Time to first relapse • Number of relapses • Reduction/cessation in systemic steroid use	Some Concerns The EAG believe the CS included all related outcomes in the modelling, except for the AEs related to the IS treatment, benralizumab treatment and EGPA-specific complications/ adverse events. The EAG have some concerns regarding the impact

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Use of IS • Vasculitis activity scores • Pulmonary function • AEs of treatment • HRQoL	of excluded AEs on the cost and HRQoL. See Section Adverse events4.2.5
Perspective on costs	National Health Service (NHS) and Personal Social Services (PSS) perspective	Appropriate The perspective is the same as the reference case.
Type of economic evaluation	Cost effectiveness of treatments in terms of incremental cost per quality-adjusted life year	Appropriate The company presented cost-utility analysis.
Time horizon	Sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	Appropriate A lifetime horizon was used for the cost-effectiveness analysis. This was considered to be appropriate by the EAG.
Synthesis of evidence on health effects	There is a preference for RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available. Identified based on systematic review Synthesis of outcome data through meta-analysis	Appropriate The synthesis of evidence on health effects complied with the reference case. In the absence of a head-to-head trial, based on the data from MANDARA¹ and MIRRA,⁶⁴ Bucher ITC was conducted by the company to estimate the relative efficacy of benralizumab versus SoC. For a critique of the evidence synthesis, see Section 3.3. For commentary on the use within the economic model, see Section 4.2.2.
Measuring and valuing health effects	Quality of life to be presented in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Appropriate To inform HRQoL data in the model, the utility values derive from EQ-5D-5L-mapped to EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Appropriate The company used utility values obtained from the Adelphi DSP, in which patients completed the EQ-5D Questionnaire.³ In scenario analysis, utility values obtained from UK vignette valuation

Element of health technology assessment	Reference case	EAG comment on company's submission
		from the perspective of patients and the general population were used. ³⁸
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Appropriate EQ-5D values were scored in accordance with NICE guidance. ⁶⁶
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Appropriate The CS states that this technology does not qualify for a NICE severity modifier based on a QALY shortfall analysis. The EAG agrees with this.
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	Appropriate Unit costs were appropriately obtained from eMIT, ⁶⁷ NHS reference costs, ⁶⁸ PSSRU unit costs ⁶⁹ and BNF. ⁶⁸
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Appropriate Discounting of costs and outcomes was in line with NICE guidelines. ⁶⁶
Source: Company submission document B, Table1⁵ Abbreviation: EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; EGPA = eosinophilic granulomatosis with polyangiitis; Adelphi DSP = Adelphi Disease Specific Programmes; HRQoL = health related quality of life; QALY = quality adjusted life-year; RCT; randomized control trial; CUA = cost utility analysis; BNF = British National Formulary; eMIT = Drugs and pharmaceutical electronic market information tool; EQ-5D = European Quality of Life-5 Dimensions; AE = adverse event; CYC = cyclophosphamide; IS = immunosuppressant; NHS = National Health Service; OCS = oral corticosteroids; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; RTX = rituximab; SoC = standard of care; UK = United Kingdom; MA = Marketing Authorisation.		

4.2.1 Model design and assumptions

This section reviews the model design and assumptions, Table 4.3 details whether the methods are considered appropriate, some concerns or key issues. Following subsections elaborate on the issues.

Table 4.3: Summary of EAG's critique on the design of the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Type of model	B.3. p.66	Appropriate A Markov state-transition model was used by the company.
Model structure/ health states	B.3.2.2, pp.69-78 B.3.2, Table 29, p.67	Appropriate The EAG considers the model structure/design to capture the major outcomes associated with the use of benralizumab. The model structure/design is described in Section 4.2.2. The 4-week cycle length Markov model developed by the company comprising three alive EGPA disease states including remission, stable disease and relapse along with a death state. The company also considered and incorporated a sub-model with a same cycle length (4 weeks) referred as OCS sub-model to modeling impact of acute and chronic AES related to the OCS treatment and the impact of reducing OCS use on patients' HRQoL and NHS costs utilizing a recently published study by Gibson et al. 2024 on modelling AEs related to OCS treatment and benefits of OCS-sparing in long-term. ⁷ Key Issue 4 There are assumptions implicit in the model that the company does not explicitly state regarding: restarting OCS after discontinuation of benralizumab; the likelihood of discontinuing benralizumab for people who discontinue OCS and those who do not; and the effectiveness of SoC with OCS vs SoC without OCS. See Sections 4.2.2.3 and 4.2.4.4.

Baseline population characteristics	B.3.2.1, p.69 B.3.3.1, p.84	Appropriate CPRD⁸ was used by the company as a representative source of UK clinical practice to derive baseline characteristics of patients entering the model as well as the proportion of patients in chronic comorbidities defined in the OCS sub-model. The EAG are satisfied with baseline population characteristics
Treatment effectiveness	B.3.3.2, pp. 84-89 Appendix D B.3.4, pp.95-101 B.3.8.2, Table 64, p.112 B.3.2, Table 29, p.67	Some concerns Please see the Effectiveness section 3.3 for concerns regarding the effectiveness estimates derived from the Bucher ITC analysis, particularly around the transitivity assumption. Some concerns In the CS economic model, the annualised rate of relapse (ARR) is based on the transitions from both stable and remission states to relapse, and the ARR is applied to both the stable to relapse and remission to relapse transitions. While this is a simplification, the EAG believes that the small sample size of transitions from the remission state makes this simplification reasonable. There is the same concern regarding the estimation and application of the odds ratio of remission in the economic model. More details are provided in Section 4.2.4.24.2.3.3.
Treatment waning	B.3.3.2, P.86 B.3.2, Table 29, p.67 B.3.8.2, Table 64, p.113	Key Issue 6 No treatment waning effect was included in the model. The company indicated that this assumption was validated by clinical experts and also consistent with an evaluation of benralizumab for severe eosinophilic asthma in TA565.⁶ The EAG accepted this assumption. However, it has added it as a Key Issue to highlight to the committee the importance of this assumption to the ICER estimate. The effectiveness estimates (and sources) assumed to be sustained are: - The odds ratio of response (ITC estimate) - The annualized relapse rate (ITC estimate) - The reduction in percentage of stable patients who are refractory (MANDARA trial)
Treatment stopping rules	B.3.3.5, page 89	Key Issue 2 There is uncertainty regarding the benralizumab discontinuation rate as there is a significant difference in estimates from MANDARA¹ (█%) and alternative

		real-world sources on using benralizumab (from █% to █%). The company used a █ per year in the economic model as a conservative assumption, validated by clinical experts to be reflective of UK clinical practice.⁹ See Section 4.2.7.1 Error! Reference source not found. for more details.
Baseline transition probabilities and proportion refractory/non-refractory	B.3.3.2, pp. 84-89 B.3.2, Table 29, p.67 B.3.3, Table 33, p.82 B.3.8.2, Table 64, p.113	Appropriate Transition probabilities of the benralizumab arm were derived from MANDARA.¹ Two transition matrices were applied in the model for benralizumab: one for 0-52 weeks and one for responders beyond 52 weeks. In the SoC arm, pre-response transition probabilities were adjusted by the OR of remission and the ARR of relapse derived from the Bucher ITCs. More details on estimating transition probabilities are provided in Section 04.2.3.2 and Section 4.2.3.3. Appropriate The initial proportion of patients in the stable disease state who are refractory was obtained from CPRD and used in both arms of the model (█%).⁸ It was assumed constant in the SOC arm over time. The company applied risk reduction informed by MANDARA¹ (█%) to the proportion of patients in refractory state at Week 52 in benralizumab arm. The company conducted a scenario analysis by varying the starting proportion by +/- 5%. See section 4.2.3 4.2.3 for more details. Some concerns The mortality estimates in the model included EGPA state mortality hazard ratios, which remained constant over time. The EAG observed that this would not account for change in mortality over time related to increasing risk of OCS chronic events as time went on. In the CS model, mortality rates increased as the SMRs were applied to increasing population hazard rates. However, there is no mechanism in the model

		by which the effect of the intervention on OCS complications results in changes in mortality. See Section 4.2.3.5.
Adverse events/ complications (especially OCS)	B 3.3.6, p. 91 - 95	Appropriate The OCS adverse events were modelled as an OCS sub-model in the cost-effectiveness analysis. This approach captures the comorbidities associated with chronic OCS use and the benefit of OCS sparing in patients. See Section 4.2.5 for more information. Some Concerns IS adverse events were excluded from the model. These are likely different to adverse events associated with OCS due to a different mechanism of action. This is likely conservative with respect to benralizumab since a patient is less likely to receive IS and therefore experience fewer IS adverse events. See Section 4.2.5 for more details.
Internal and external validity	B, 3.13, p.124 Clarification letter, pp.36-40	Appropriate For internal validity, economic model structure, inputs and assumptions were validated by the company through obtaining feedback from clinical experts⁹ and health economic experts in the UK.⁷⁰ For external validity, in response to the clarification letter, the company provided more detail on how the company validated the model predictions in the absence of external patient data.¹⁶ The EAG acknowledge that the company clinical experts accept the model predictions as reasonable. However, there is uncertainty in the long-term outcomes. See section 5.5 for more details.
Source: Company submission document B⁵; clarification letter¹⁶ Abbreviations: CS = company submission; EAG = Evidence Assessment Group; EGPA = eosinophilic granulomatosis with polyangiitis; CPRD = Clinical Practice Research Datalink; HRQoL = health related quality of life; AE = adverse event; OCS = Oral Corticosteroids; IS = Immunosuppressant; SoC = standard of care; ARR: annualised rate of relapse; OR = odds ratio; ITC = Indirect Treatment Comparison; UK = United Kingdom; NICE = National institute for Health and Care Excellence.		

4.2.2 Model structure/design

4.2.2.1 EGPA disease model

A cohort, Markov state-transition model with a 4-week cycle length was developed by the company to assess the lifetime costs and effectiveness of benralizumab as an add-on to SoC treatment in adults with relapsing or refractory EGPA from the NHS perspective.

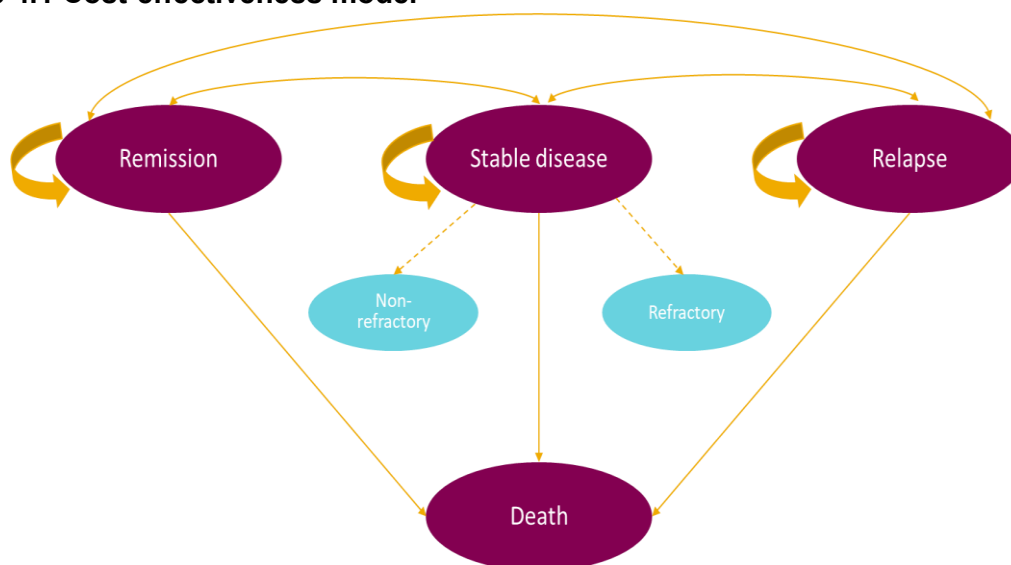
This model has two parts: the main EGPA model and OCS sub-model which will be described, respectively.

Figure shows the company main EGPA model comprising three alive EGPA disease health states including remission, stable disease and relapse along with a death state. The stable health state includes refractory and non-refractory health states. The company indicated that although the EGPA is best described by four health states (remission, refractory, non-refractory and relapse), due to limitation in data from the MANDARA trial to inform transitions to and from these states, the company considered these two health states as sub-states of 'stable disease' health state with constant proportions in each (see Section 4,2,2,1). Patients were entered in the model in the stable disease state, in line with MANDARA¹, and allowed to transition between any three alive health state of remission, stable disease and relapse, or to the absorbing state 'dead'. Further information on health states' interpretation in UK clinical practice and specific condition of each health state in terms of Birmingham Vasculitis Activity Score (BVAS) and daily OCS doses considered in the economic modelling are provided in the Table 31 in the CS⁵ and the clarification letter.¹⁶

In general, the EAG are satisfied with the developed model structure. The company provided the model structure for benralizumab and SoC treatment arm in Figure 12 and Figure 13 in the CS.⁵

After 12 months, patients receiving benralizumab were classified as responders and non-responders. Responders continued to receive benralizumab and non-responders stopped benralizumab and continued to receive SoC only. In the original CS, the percentage of responders at 12 months was used to transition patients in remission/stable/relapse states to the responder subgroup. Following a query in the clarification letter (Question B11),¹⁶ regarding benralizumab response at 52 weeks, the Company updated the model so that all patients who respond to treatment at 52 weeks (defined as remission; BVAS=0 and an OCS dose ≤ 4 mg/day) continue to receive benralizumab, while all patients in the stable or relapse states (and therefore not in remission) do not respond and therefore discontinue benralizumab treatment, going on to receive SoC..

Figure 4.1 Cost-effectiveness model



Source: CS Document B, Figure 9⁵

Footnotes: Purple boxes denote health states; blue boxes denote sub-states where patients were subject to sub-state specific utilities

4.2.2.2 The OCS model structure and other adverse events

The company did not include benralizumab-related AEs in the economic model. The reason provided by the company was the low incidence of serious AEs observed in MANDARA.¹ The company also did not incorporate AEs related to IS treatment. However, the company considered AEs related to OCS use in the economic model. CPRD analysis conducted by the company on people with EGPA in England revealed that OCS were prescribed for 86.2% of people on the OCS treatment over a mean follow-up of 5.4 years post-diagnosis.⁸ The EAG acknowledges that OCS AEs are the major adverse events. Also, if benralizumab reduces EGPA-related AEs/ complications then excluding those from the model is a conservative assumption when estimating the ICER for benralizumab.

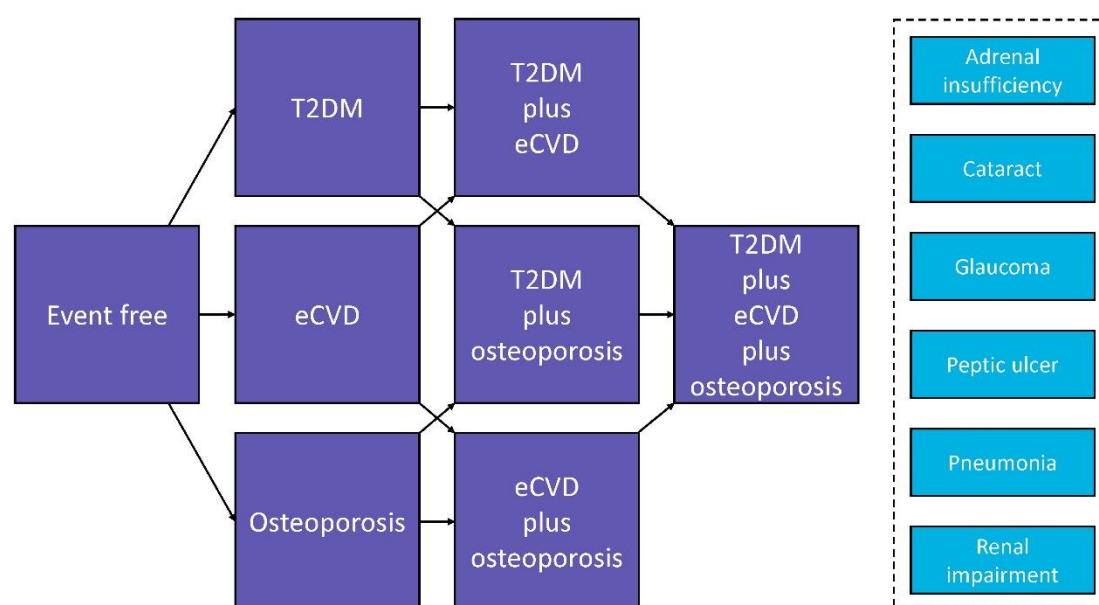
The company incorporated a sub-model, referred to as the OCS sub-model, aiming to capture impact of reducing OCS use on patients' HRQoL and NHS costs. The OCS sub-model is informed by a recently published study by Gibson et al. (2024)⁷ on modelling AEs related to OCS treatment and benefits of OCS-sparing in long-term. According to this study, use of OCS is associated with an increased risk of AEs including acute clinical events and chronic comorbidities due to cumulative lifetime OCS exposure.⁷ The company stated that their approach, adopted in the submission, allows them to capture the long-term impact of chronic conditions more effectively. They noted that in previous NICE technology appraisals,^{6,71} AEs were considered as acute events, which could result in underestimation of the long-term impact of chronic conditions.

Figure (reproduced Figure 10 in the CS)⁵ presents the OCS sub-model structure.⁵ The OCS dose is reduced when patients are receiving benralizumab and this affects the likelihood of the acute and chronic AEs (see Section 4.2.5 for information on the risks of these AEs). The cohort starts in the model as either event-free or in one of the three chronic disease states (T2DM, eCVD, or osteoporosis). Over time, patients could progress to OCS-associated chronic events, including combinations of T2DM, eCVD, and osteoporosis. Additionally, patients are at risk of experiencing six acute AEs including adrenal insufficiency, cataract,

glaucoma, peptic ulcer, pneumonia, renal impairment, which were modelled as “one-off” events lasting one cycle. The risk of OCS-associated acute events and the risk of developing OCS-associated chronic events increases with accumulated OCS dose.

For more details, please see Sections B.3.2.2 and B.3.3.6 in the CS.⁵

Figure 4.2 OCS-sub model structure



Source: CS Document B, figure 10⁵

Footnotes: Purple boxes relate to chronic disease health states; blue boxes relate to acute events.

Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroid; T2DM = type-2 diabetes mellitus

NB: In the Gibson et al, 2024 publication, adrenal insufficiency was effectively modelled as a fourth chronic comorbidity (alongside T2DM, eCVD and osteoporosis).⁷ Adrenal insufficiency was not included in the OPRI study, therefore the parametrisation of incidence as a function of cumulative OCS was unknown.⁷² In light of this, a simplified approach was adopted to model adrenal insufficiency as an acute event in the OCS sub-model; the incidence of the event was informed by a targeted literature search, a one-off cost was applied in the cycle of incidence, and no disutility was applied as a conservative assumption, in absence of data reported from Gibson et al., 2024 publication⁷

4.2.2.3 Key OCS and benralizumab discontinuation assumptions

The company model makes the following assumptions with associated consequences:

The following related assumptions were implicitly made in the model:

- (1) Patients who discontinue OCS in the benralizumab arm never restart OCS after discontinuing benralizumab. This leads to a much lower percentage receiving OCS as part of SoC after benralizumab than in the SoC arm of the model.
- (2) The proportion of responders is the same for those who do not discontinue OCS while on benralizumab and those who do discontinue OCS while on benralizumab. The benralizumab discontinuation rate is the same for those who do and those who do not discontinue OCS.

A consequence of these assumptions is:

- The percentage of patients receiving SoC after benralizumab discontinuation who received OCS is continually decreasing.

This leads to the following assumption implicit in the CS model:

- (3) The relative risk of SoC with OCS vs SoC without OCS = 1. The transition probabilities for SoC are the same regardless of the percentage of patients receiving OCS. See Section 4.2.4.4.

The assumptions (1), (2) and (3) contribute to the following consequence:

- The greater the rate of benralizumab discontinuation, the lower the ICER for benralizumab. This is because SoC after benralizumab dominates SoC (greater QALYs and lower cost). The effectiveness of SoC with OCS is the same as SoC without OCS.

The EAG believes that OCS is considered important treatment as part of SoC. It likely has an effect on remission, stable and relapse states. The EAG explores alternative assumptions in the EAG analyses.

4.2.2.4 Treatment stopping rules

Benralizumab

The company defined the benralizumab stopping rule based on the response to the treatment which was conducted at 52 weeks in the model.^{5,16} The company indicated that response assessment at week 52, is in line with anticipated use of benralizumab in EGPA in UK clinical practice,⁹ length of the MANDARA trial¹ and the recommended use of benralizumab in severe asthma.

It was assumed by the company that all patients who respond to the treatment will continue to receive benralizumab for the rest of their lifetime except for those who discontinue based on general attrition rates and non-responders will discontinue benralizumab and receive SoC. It was also assumed that patients who discontinued benralizumab treatment were no longer eligible to switch to benralizumab at any subsequent timepoint. EAG found these assumptions appropriate.

In addition, a discontinuation rate for benralizumab was assumed that was applied at a constant rate monthly from the start of the model and ongoing over the model time horizon (see Section 4.2.7).

OCS

In the SoC arm of the model, the percentage of patients receiving OCS was assumed to be constant over time at 86.2%. In the benralizumab arm of the model, OCS use was assumed to discontinue as a rate of ■% per year. See Section 4.2.7.1.

4.2.3 Baseline transition probabilities and proportion of patients in refractory sub-state

4.2.3.1 Proportion of patients who are refractory in the stable disease state

For the purpose of capturing a difference in HRQoL between refractory and non-refractory patients, a percentage of patients in the stable state were classified as refractory and non-refractory. The percentage of patients who are refractory in the stable state in the benralizumab arm was obtained from MANDARA¹ (■%). Due to absence of data from the MANDARA trial¹ to inform the proportion in the SoC arm, the company used the CPRD dataset⁸ which stayed constant (■%). The company assumed the initial proportion of patients in the refractory sub-state in the benralizumab arm was ■% at the start of the model, the same as the SoC arm. This assumption was made for two reasons: to maintain consistency between the two arms and because CPRD data was considered the best representation of current clinical practice.⁵ After 1 year, the risk reduction informed by MANDARA¹ (■%) was applied to the proportion of patients in refractory state at Week 52 in benralizumab arm. The company conducted a scenario analysis by varying the starting proportion by +/- 5%.⁵

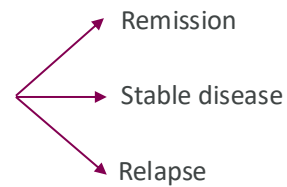
The EAG requested that the company clarify how patients were classified by disease state. In response to the clarification letter it was indicated by the company that the refractory state was defined as “Not in Remission in current assessment period, plus not in Remission in the prior assessment period (at index date) i.e. over 6 months”. CPRD disease state definitions (PfC, Table 1),¹⁶ stable disease state definitions and stratifying to refractory and non-refractory (PfC, Table 2 and Figure 3)¹⁶ were provided by the company in the clarification letter.¹⁶ Please see the Figure reproduced Figure 3 in clarification letter.¹⁶

Figure 4.3 Classification of patients in disease states from CPRD

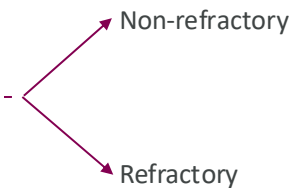
Step 1: Classification of patients into 3 mutually exclusive states

At each measurement

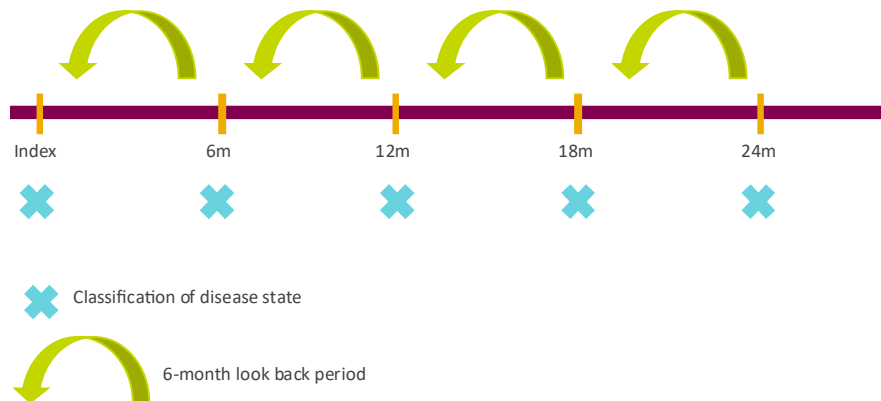
- Patients categorised into remission, stable disease or relapse based on the previous observation period
- Patients stay in that category till next observation period



Step 2: Stratifying 'stable' patients into "non-refractory" and "refractory" states



This stage of the analysis can only be performed from month 6 onwards, as refractory patients are defined as not having achieved remission in the last 6 months



Source: PfCs, Figure 3¹⁶

Footnote: The illustration of Step 1 is shown only for the first 24 months (look-back period 6 months); for the subsequent years 3–5, the look-back period is 12 months

Abbreviations: CPRD = Clinical Practice Research Datalink; m = months; PfCs = Response to points for clarification letter

4.2.3.2 Transition probabilities in benralizumab arms

Transition probabilities between EGPA states in the benralizumab arm were derived from 4-weekly transition count data from MANDARA¹ and were presented in Table 37 in the CS. As the effectiveness estimate for response was derived from 12-month timepoint data and because it was assumed that response at 12-months would be a benralizumab stopping rule in clinical practice, transition probabilities were estimated separately for the first 12 months and the subsequent time period.

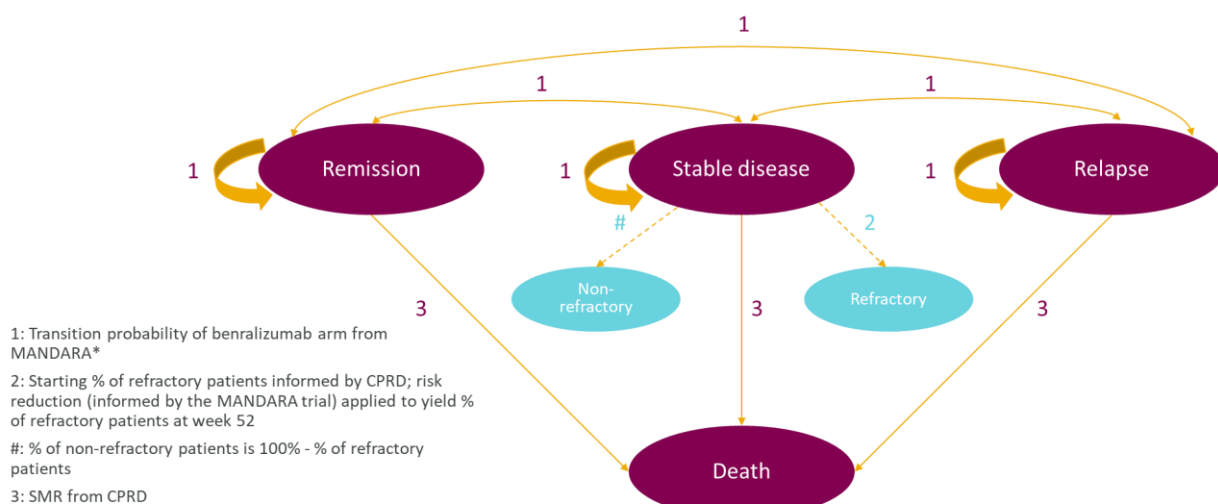
First year transition probabilities for benralizumab arm derived from MANDARA¹ including all patients from weeks 0-52 in the benralizumab arm before the time of response assessment at week 52 (BVAS=0 and an OCS dose ≤ 4 mg/day).

Beyond 1 year, transition probabilities for benralizumab arm derived from MANDARA¹ including patients who respond to the treatment based on the response assessment (BVAS=0 and an OCS dose ≤ 4 mg/day). These transition probabilities were assumed to be constant in the economic model over time after 52 weeks. The company indicated that this assumption is consistent with the no waning effect assumption in TA565 on benralizumab for severe eosinophilic asthma.⁶ Transition probabilities for non-responders were the same as those for people receiving SoC.

More details on the approach used by the company to inform are transition probabilities in the economic model was provided in the Appendix 1 of clarification letter.¹⁶

The Figure reproduced Figure 18 in clarification letter to present model parameterisation for benralizumab.¹⁶

Figure 4.4 Model structure parameterisation by benralizumab arm



*For first 52 weeks, transition probabilities are informed by all patients in the benralizumab arm until the time of response assessment. Following response assessment (week 52), transition probabilities for responders are informed by subgroup of responders in benralizumab arm (non-responders discontinue treatment with benralizumab)

Source: PfCs, Figure 18¹⁶

Abbreviations: CPRD = Clinical Practice Research Datalink; SMR = standardised mortality ratio

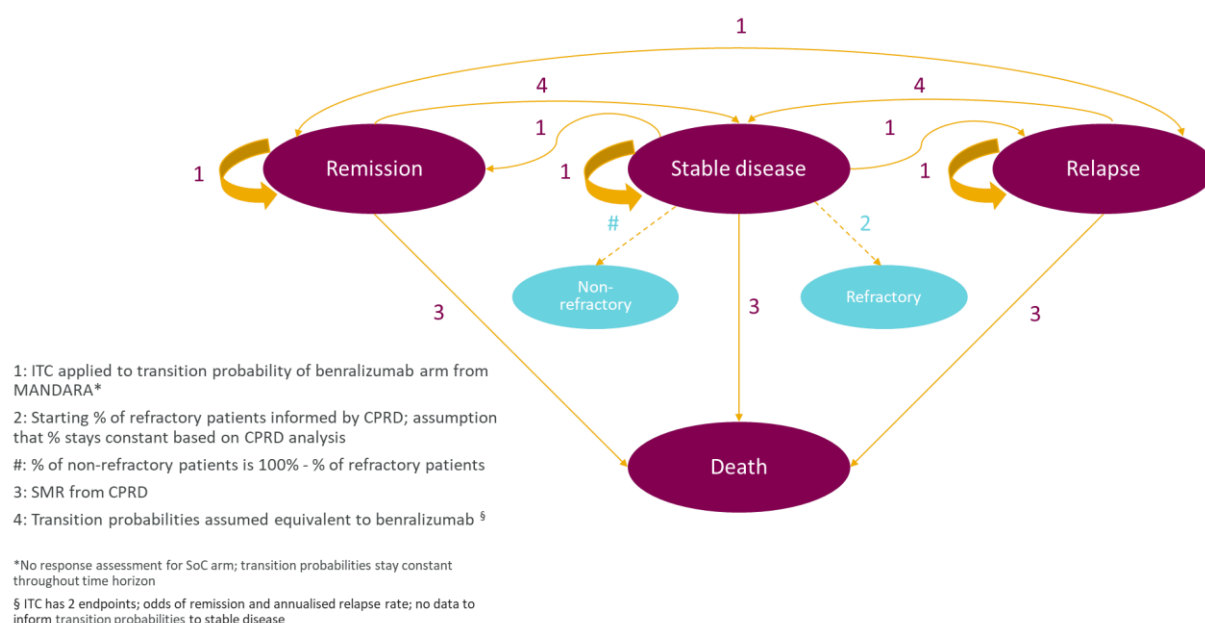
4.2.3.3 Transition probabilities in SoC arms

Transition probabilities in SoC arm -week 0 onwards- were presented in Tables 39 of the CS and applied to the model from week 0 onwards.⁵

In the SoC arm, OR and RR derived from Bucher ITC study (Table 38 in the CS) ⁵ used to adjust pre-response transition probabilities of benralizumab arm. The company assumed SoC transition probabilities constant over time.

The EAG found an error in the diagram presenting model structure parameterisation in SoC arm (Figure 13) which represent 2 arrows going from relapse to stable and no arrows going the other way. The company provided an updated diagram in clarification letter. The Figure reproduce the updated model (Figure 7) in the clarification letter.¹⁶

Figure 4.5 Model structure parameterisation by SoC arm



Source: PfCs, Figure 13¹⁶

Abbreviations: CPRD = Clinical Practice Research Datalink; ITC = indirect treatment comparison; SMR = standardised mortality ratio; SoC = standard of care

Moreover, EAG noted that in the economic model, the annualised rate of relapse is based on the transitions from both stable and remission states to relapse and the annualised relapse rate is applied to both the stable to relapse and remission to relapse transitions. While this is a simplification, the EAG believes that the small sample size of transitions from the remission state makes this simplification reasonable.

4.2.3.4 Informing and incorporating risk of OCS-adverse events

To estimate risk of incidence of acute AEs-modelled using incidence- and developing chronic disease - modelled using prevalence- as a function of cumulative OCS dose, Cox proportional hazard regression models were used by the company.⁵ The mean daily dose for each health state was informed by CPRD data.⁸ See Section 4.2.5 for more detail on adverse events.

The risk of AE was defined by the following formula⁷:

$$\text{OCS AE Risk}_{\text{cycle}} = 1 - e^{-c * \text{gen}_{\text{risk}} * (\text{OCS}_{\text{HR}})^{\text{OCS}_{\text{dose}}}}$$

The baseline event rates were sourced from Gibson et al., 2024⁷ which represented the risk of developing the comorbidity in the general

population with no prior OCS treatment. The coefficient represented the cumulative OCS dose when one gram was increased in the dose. Then it was exponentiated to obtain the increased risk developing comorbidity per gram of cumulative OCS dose as hazard ratios. Hence, the mean risk of developing a comorbidity in the patients was derived using the regression model and the weighted average of cumulative OCS dose of patients residing in the health states across the cohort. For more details on the inputs which were used to estimate of risk of chronic disease onset, chronic disease progression, and acute events onset including mean morbidity rate, mean event rate, coefficient per 1g cumulative dose, HR (relative to general population), mean daily dose for each health state, see CS Section B.3.3.6.⁵

OCS accumulation is affected by both the numbers receiving OCS and OCS dose received in each of the EGPA states (remission, stable, relapse). The effect of different OCS discontinuation assumptions in the model on numbers of patients with different chronic conditions after 20 years is presented in Table 4.4. Scenarios with different assumptions regarding OCS use are explored in the EAG analyses.

Table 4.4: Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort

OCS discontinuation rate	T2DM	eCVD	OP	T2DM/eCVD	T2DM/OP	eCVD/OP	T2DM/eCVD/OP
37.96% per year	61.2	81.8	50.6	48.9	23.7	24.4	20.8
0% per year	58.7	83.0	57.2	63.2	31.9	34.8	24.1
37.96% first year, 0% subsequently	60.8	82.4	52.5	52.8	25.8	27.0	21.6
Source: EAG base-case Excel Model							

4.2.3.5 Mortality

No mortality is captured by the MANDARA trial.¹ The risk of all-cause mortality was estimated using UK national life tables (2020–2022) stratified by age- and sex. The standardised mortality ratio (SMR) for each health state was informed by UK-specific CPRD data. The CPRD analysis showed that mortality rates are higher in patients with EGPA compared to the general population in England. The following table shows the SMRs for each health state used by the company in the economic model.⁵

It should be mentioned that the company model did not investigate the OCS-related mortality in the OCS sub-model. Since investigating OCS-related mortality needs long-term follow up, the EAG are satisfied with the company approach. However, the EAG did some exploratory analysis using OCS chronic event mortality hazard ratios obtained from Gibson et al.(2024)⁷ the same source as the OCS risk model.

Table 4.5: Mortality inputs

Disease state	Mean	Lower CI	Upper CI	Source
SMR in remission (relative to general population)	■	■	■	CPRD ⁸

Disease state	Mean	Lower CI	Upper CI	Source
SMR in stable disease (relative to general population)	■	■	■	
SMR in relapse (relative to general population)	■	■	■	
Source: Table 28, PfCs ¹⁶ Abbreviations: SMR = Standardised mortality ratio; CI = confidence interval; CPRD = Clinical Practice Research Datalink.				

4.2.4 Treatment effectiveness

4.2.4.1 Odds ratio of remission (benralizumab vs SoC)

Benralizumab affected clinical outcomes in the model in two ways: (1) through increasing the percentage of patients in the remission state, and reducing the percentage of patients in the relapse state, (2) reducing the use of OCS while on benralizumab. Effect (1) changed costs and QALYs through the EGPA state average costs and utilities. Effects (1) and (2) changed costs and QALYs through the reducing the cumulative OCS dose patients received over time and thereby reducing the likelihood of OCS acute and chronic events. The effect of benralizumab on the EGPA disease states was based on two effectiveness estimates versus SoC: the odds ratio of remission at 12 months and the annualised relapse rate ratio (ARR) at 12 months. These estimates were derived using a Bucher ITC (see Section 3.3).

4.2.4.2 Annualised relapse rate ratio (benralizumab vs SoC)

The ARR statistic uses relapse at 12 months as the outcome variable. Patients who are in relapse may have previously been stable or in remission (most were stable). The ARR is applied to both the stable to relapse and remission to relapse transitions. While this is a simplification, the EAG believes that the small sample size of transitions from the remission state makes this simplification reasonable. There is the same concern regarding the estimation and application of the odds ratio of remission in the economic model.

4.2.4.3 Reduction in refractory patients (benralizumab vs SoC)

The company makes the assumption that the percentage of stable patients who are refractory reduces from ■% to ■% after one year and then it remains constant.

4.2.4.4 SoC with OCS vs SoC without OCS

The SoC treatment following discontinuation of benralizumab (Ben_SoC) is modelled to have an ever-decreasing percentage of patients receiving OCS treatment. However, the transition probabilities for Ben_SoC are modelled to be the same as for SoC. This is equivalent to assuming the relative risk of SoC with OCS vs SoC without OCS = 1.

The EAG does not have any evidence for the relative risk of improving EGPA state for SoC with OCS vs SoC without OCS. The EAG explores alternative relative risk of SoC with OCS vs SoC without OCS estimates in the EAG scenario analyses.

4.2.5 Adverse events

Benralizumab was a treatment that was well tolerated in EGPA patients in the MANDARA trial³⁶, and a low incidence of serious adverse events (AEs) was observed. Also, there was no clinically significant difference in the proportion of patients who reported AEs and serious adverse events (SAEs) between the two treatment arms in the DB period. This indicated that the impact of benralizumab-related AEs on the quality of life and cost is minimal. Hence, the benralizumab-related adverse events were not included in the cost-effectiveness analysis. The EAG is of the opinion that this was a reasonable assumption.

The AEs and chronic comorbidities associated with long-term use of OCS in EGPA was modelled to inform the impact on cost and quality of life. The OCS sub-model helped to inform the effect of benralizumab on OCS-sparing, thereby reducing the risk of developing adverse events in EGPA patients. The common chronic comorbidities associated with OCS treatment were T2DM, Cardiovascular disease (eCVD) and Osteoporosis. These were modelled as health states using prevalence in the model. The acute events were Adrenal insufficiency, Cataract, Glaucoma, Peptic ulcer, Pneumonia, Renal impairment. These were modelled as incidence of acute events with the effects lasting for the length of the cycle. See Section 4.2.3.4 for the risk equation.

IS adverse events were excluded from the model. These are likely different to adverse events associated with OCS due to a different mechanism of action. This is likely conservative with respect to benralizumab since a patient is less likely to receive IS and therefore experience fewer IS adverse events.

4.2.6 Health-related quality of life

Table 4.6: Summarises the EAG's critique on HRQoL within the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Identification of HRQoL data within the SLR	Appendix H, p. 101-128	Appropriate An appropriate range of databases were used for searching relevant studies. But, because of the rarity of the disease, an appropriate HRQoL data source for EGPA patients were not found in the search. See Section 4.1 for more details.
Remission/non-refractory/refractory/relapse health state utility values	B.3.4.4, p.98-102	Appropriate The MANDARA trial used SF-36 to collect EGPA health state utility data from patients to inform their HRQoL. When these values were mapped to EQ-5D-3L, as prescribed in the NICE reference case, the values did not represent experience in the clinical setting in the UK. ³⁶ So, to inform the HRQoL data, two real world studies were conducted: Adelphi DSP study and UK-specific vignette study. ^{3,38} The Adelphi DSP study used EQ-5D-5L to generate the utility scores of EGPA patients and these utility

		scores were cross-walked to EQ-5D-3L using UK tariff to make it suitable for UK decision making.³ The health state utilities from this study were used to inform the HRQoL of patients in the model because the results satisfied face validity checks. The EAG thinks the Adelphi DSP study was the best source of evidence for the cost-effective analysis. Key Issue 2 The patients included in the Adelphi DSP study suffered from adverse events which could overlap with OCS-associated acute and chronic adverse events. This could lead to underestimates of utility values for patients in the refractory and relapse states relative to the remission and non-refractory states.
OCS and IS treatment adverse events/ complication disutilities	B. 3.4.5, p. 101-102.	Appropriate OCS-associated acute and chronic events were included in the CS model. The common chronic comorbidities - T2DM established, cardiovascular (eCVD) and osteoporosis – were included as health states. The acute events like Adrenal insufficiency, Cataract, Glaucoma, Peptic ulcer, Pneumonia, Renal impairment was captured as 'one-off' events in the model. The utility decrements associate with the complications were appropriately sourced from Sullivan et al., 2011⁷³ See Section 4.2.6.1 for details. Some Concerns IS adverse events were excluded from the model. These are likely different to adverse events associated with OCS due to a different mechanism of action. This is likely conservative with respect to benralizumab since a patient is less likely to receive IS and therefore experience fewer IS adverse events. See Section 4.2.6.2.
Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; HRQoL = Health-Related Quality of Life; SLR = Systematic Literature Review, SF-36 = Short Form-36, EQ-5D = Euro QoL – 5 Dimension 3 Level, EGPA = Eosinophilic granulomatosis with polyangiitis, OCS = Oral Corticosteroids, NICE = National Institute for Health and Care Excellence, Adelphi DSP = Adelphi Disease Specific Programme, EQ-5D-5L = Euro QoL – 5 Dimension 5 Level, T2DM = Type 2 Diabetes Mellitus; eCVD = established cardiovascular disease; IS = immunosuppressants; UK = United Kingdom.		

4.2.6.1 EGPA state utility estimates

The utility scores generated in the MANDARA trial was deemed not suitable to reflect the UK clinical setting. They were generated using SF-36 and then mapped to EQ-5D-3L which was recommended by the NICE reference case.³⁶ The mapping algorithm developed by Rowen et al., 2009 was used.⁷⁴ However, the obtained utility scores lacked face validity. The results

were not consistent with the insights collected from patients and clinical experts. There was minimal utility difference between remission and relapse states, and refractory health state did not have the lowest utility value where the patients experienced despair, anxiety, frustration and significant negative impact on their wellbeing. The interviews from clinical experts, results from literature search and concerns from OMERACT Vasculitis Working Group highlighted that SF-36 may not accurately measure the physical health state of patients to capture all the important aspects of EGPA. Hence, to inform the impact of EGPA on patients' HRQoL, two new real-world studies were conducted: the Adelphi DSP study and the UK-specific vignette study.^{3,38} The utility estimates from these studies are presented in Table 4.9.

- The Adelphi DSP study: The study was conducted among 177 EGPA patients from UK (■), Germany (■), France (■), Italy (■), Spain (■), US (■). A sample size of ■ was reflected the UK clinical practice because of the low incidence of the disease. The patient demographics like mean age, gender distribution, mean body weight did align closely with the UK EGPA population in clinical expert opinion. The EQ-5D-5L was completed by the patients and the generated utility values were cross-walked to EQ-5D-3L to abide by the NICE reference case.³
- The UK-specific Vignette study: The UK-specific vignette study was conducted to generate data which was most reflective of UK EGPA patients. The vignettes were developed, and the study was conducted in accordance with the NICE DSU guidance. 8 patients with EGPA, 4 clinical experts well-versed in treating patients with EGPA and 1 HRQoL expert who is experienced with EGPA were involved in developing the vignette. The study included 300 people from the general population and 21 EGPA patients. The participants used EQ-5D-5L questionnaires to inform HRQoL data and the utility scores were cross-walked to EQ-5D-3L using UK tariff. The value for refractory health state was unusually low when compared to the utility values of other health states and diseases, despite being rated consistently by the participants.³⁸

The utility values generated by Adelphi DSP study were deemed most appropriate to inform the cost-effectiveness model. These values represented the real-world scenario with a significant difference in utility estimates between the EGPA states with the refractory state associated with the lowest utility score. The EQ-5D-5L instrument responses were cross walked to EQ-5D-3L, which was the recommendation in NICE reference case and the most appropriate instrument and value set to evaluate changes in HRQoL in the UK setting. The average utilities in the model are likely underestimates at the beginning of the model and likely overestimates later on in the model.

Out of 177 patients, ■ patients in the Adelphi DSP study suffered from various organ damage (**Error! Reference source not found.**), which are severe adverse events, due to EGPA and the treatment received. The distribution of organ damage is presented in Table 4.9. The EAG considered that there was a significant risk of overlap for these with the OCS acute and chronic events. Disutilities for OCS comorbidities were included in the model, so the EAG has some concerns about double counting the effects of OCS adverse events. It is possible that the EGPA state utility estimates are underestimates. The distribution of OCS acute and chronic events across EGPA states was not reported.

The EAG incorporated a change to EGPA state utilities in the EAG base case. The EAG made the assumption that those in the stable and relapse states are more likely to have organ

damage than those in the non-refractory and remission states, the EAG increased the utility in the refractory and relapse states by ■■■, the average disutility across all of the acute and chronic events. It makes the simplifying assumption that everyone in refractory and relapse states in the Adelphi DSP study has one and only one acute or chronic OCS event in equal numbers, and that no-one in the remission and non-refractory states in the Adelphi DSP study has an acute or chronic OCS event.

■■■ out of the 177 patients were below 18 years of age and the minimum age included in the study was ■ years. See Table 4.7 and Table 4.8 for further details. The evidence on the appropriateness of using EQ-5D in children is unclear.³ Health state utility values by source are reported in Table 4.10.

Table 4.7: Patients with organ damage in the Adelphi DSP Study

Organ damage (grouped), n	177
Yes	■■■
No	■■■
All organ damage this patient suffers with predates their EGPA	■■■
Source: Adelphi DSP Study ³ Abbreviations: EGPA = Eosinophilic granulomatosis with polyangiitis	

Table 4.8: Breakdown of patients with organ damage in Adelphi DSP Study

Organ damage (grouped), n	177
Pulmonary	■■■
Musculoskeletal	■■■
Skin/Mucous membranes	■■■
ENT	■■■
This patient does not suffer with any organ damage	■■■
Neuropsychiatric	■■■
Gastrointestinal	■■■
Renal	■■■
Cardiovascular	■■■
Ocular	■■■
All organ damage this patient suffers with predates their EGPA	■■■
Peripheral vascular disease	■■■
Other	■■■
Source: Adelphi DSP Study ³ Abbreviations: ENT = ear nose throat, EGPA = eosinophilic granulomatosis with polyangiitis	

Table 4.9: Health state utility values

Health state	Adelphi DSP Utility value		Vignette Study utility values	
	Mean	SE	General Population valuation	Patient valuation
Remission	████	████	████	████
Non-refractory	████	████	████	████
Refractory	████	████	████	████
Relapse	████	████	████	████
Source: CS Document B Section B.3.4.4, p.100 ⁵ Abbreviations: SE = standard error; CS = company submission; Adelphi DSP = Adelphi Disease Specific Programme.				

4.2.6.2 OCS morbidity/event disutilities

The OCS complications were captured in the OCS sub-model. The acute adverse events occurred only as a cycle of incidence. So, a one-off utility decrement was applied in the same cycle. The utility decrements for chronic complications were input as annualised decrements and scaled to 28-day decrements (see Table 4.11). When a patient experienced multiple AEs, a multiplicative approach was adopted to combine the effects on the quality of life. The EAG considers that this method could account for the long-term effect of OCS treatment and the benefit of OCS-sparing by the treatment on the patient's quality of life.

The use of IS therapy is associated with adverse events that can be mild, moderate or severe and can have clinically significant impact on the quality of life of the patients. These adverse events were not modelled.

Table 4.10: Disutility values in the OCS sub-model

Morbidity or Event	Utility value	SE	Source
Chronic Disease			
T2DM	-0.062	0.0038	Adelphi DSP ³
eCVD	-0.087	0.0155	
Osteoporosis	-0.042	0.0063	
Acute events			
Adrenal insufficiency	████	████	Assumption
Cataract	-0.027	0.0060	Sullivan et al., 2011 ⁷³
Glaucoma	-0.028	0.0063	
Peptic ulcer	-0.055	0.0140	
Pneumonia	-0.079	0.0420	
Renal impairment	-0.096	0.0115	
Source: CS Document B Section B.3.4.5, Table 55, p.101-102 ⁵			

Morbidity or Event	Utility value	SE	Source
Abbreviations: SE = standard error, CS = company submission, Adelphi DSP = Adelphi Disease Specific Programmes, T2DM = Type 2 Diabetes Mellitus; eCVD = established cardiovascular disease.			

4.2.7 Resources and costs

Table 4.11: Summary of EAG's critique on resources and costs within the economic model

Aspect of model	Section in CS where methods are reported	EAG's assessment
Resource use and cost data identified in the SLR	Appendix I, p.129-146	Appropriate The company undertook extensive SLR for identifying data on resource use or cost in EGPA. The disease being rare or of low incidence, the EAG find it reasonable that the company could not find any data from the literature search.
Time on treatment	B.3.3.5, p. 89 - 90	Key Issue 2 The rate of treatment discontinuation of benralizumab (■%) was unusually low in the MANDARA DB trial when compared to that observed in the real world. Alternative sources showed discontinuation rates ranging from ■% for benralizumab treatment. The company assumed a ■% discontinuation rate, adopting a conservative approach in the model. To explore the possible effects of a higher treatment discontinuation rate on the incremental cost-effectiveness, a scenario of ■% discontinuation rate was explored in the model. But, according to EAG, there were not enough clear evidence to support this assumption and it is a key issue. See Section 0 for further information. Appropriate The patients stopped receiving benralizumab when they were no longer responding to the treatment. These patients continue to receive the standard of care treatment and no residual treatment effect was assumed from benralizumab. This assumption was followed in previous TA submissions and was validated by the clinical expert that it represented the UK clinical practice.
Dose	B. 3.2.3, p.79 – 80, B. 3.5.1, p. 103-104	Appropriate The treatment dose was appropriately informed by the MANDARA trial and validated by UK clinical experts. benralizumab was administered as 30 mg pre-filled pen SC injection Q4W. The doses and treatment distribution of OCS (Prednisolone) and IS (Azathioprine, Mycophenolate

		mofetil, Methotrexate) were sourced from the CPRD data and validated by clinical expert opinion on reflecting the UK clinical practice. The dose of OCS varied depending on the health state the patient were in, the symptoms and disease progression.
Acquisition costs	B. 3.5.1, p. 103 - 104	Appropriate The patients in the benralizumab arm incurred cost of benralizumab and the SoC treatment that they were receiving. Upon discontinuation of benralizumab, the patients ceased to accrue the treatment cost of benralizumab but incurred the treatment-related cost of SoC. The acquisition cost of benralizumab was informed by the BNF, which is an appropriate source for treatment cost in the UK setting. In the comparator arm, patients received OCS and IS, which was informed by the data on UK EGPA patients in the CRPD database. See Table 4.12 for the treatment acquisition costs. So, the costs in the SoC arm consisted of a weighted average of OCS (Prednisolone) and IS. The OCS cost varied according to the dose received and discontinuation of treatment. The IS treatment involved a fixed cost, which was a weighted average of the costs of the three common IS therapies included in the model. The EAG found that the acquisition costs were appropriately sourced from eMIT in the CS model.
Administration costs	B.3.5.1, p. 104	Appropriate Benralizumab is a self-administered pre-filled pen and, OCS and IS were orally administered to the patients. So, no administration costs were incurred by the patients. Hence, the EAG found it appropriate that the company had not included any administration costs.
Adverse event costs	B.3.5.3, p. 107	Appropriate The model captured the adverse events and comorbidities cost associated with prolonged OCS treatment. The chronic disease health cost was input as annual costs and scaled to the 28-days cycle in the model. The acute events cost was considered as one-off cost in the cycle as it occurred only in the cycle of incidence. These health state costs, and one-off costs were informed by appropriate sources obtained through literature search. Some Concern The company did not include adverse events related to IS treatment in the cost-effectiveness analysis. While it

		was a conservative assumption by the company, the EAG thinks that it could affect the cost incurred to the patients and NHS for treating EGPA. For further explanation, see Section 0
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; DB = double-blind; SLR = systematic literature review; BNF = British National Formulary; eMIT = Electronic Market Information Tool; EGPA = Eosinophilic Granulomatosis with Polyangiitis; CRPD = Clinical Practice Research Datalink; OCS = Oral Corticosteroids; IS = Immunosuppressants; PSSRU = Personal Social Services Research Unit; Q4W = every 4 weeks; NHS = National Health Service; TARS = technology assessment reviews.		

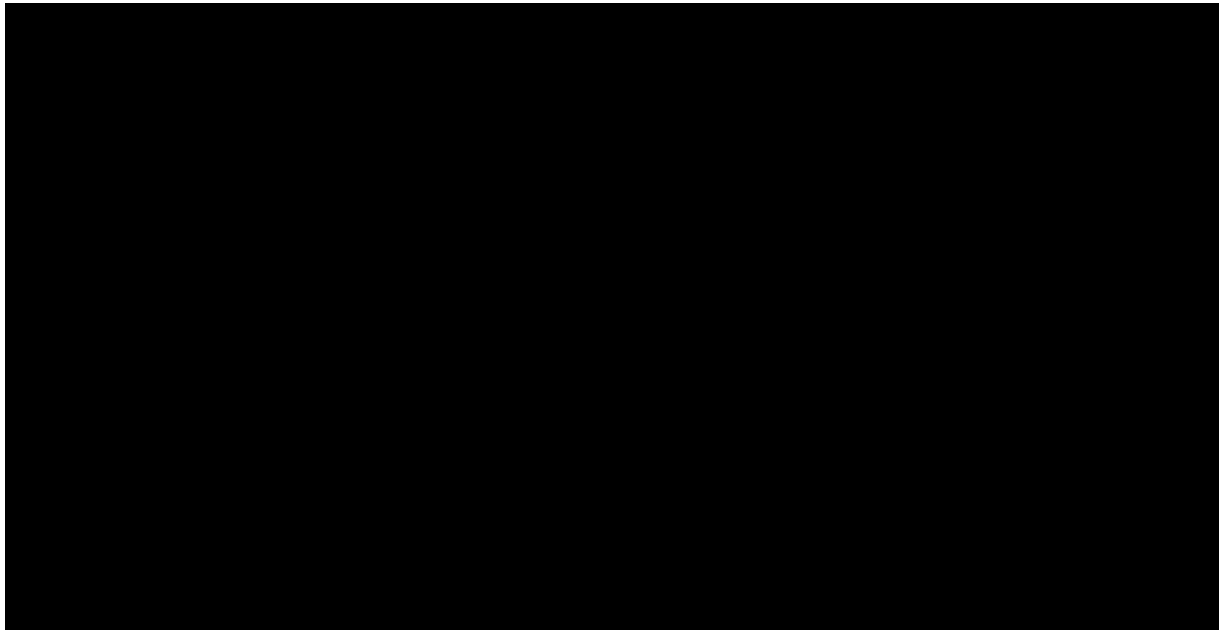
4.2.7.1 Treatment discontinuation Benralizumab

The benralizumab treatment discontinuation was based on non-responsiveness of the patients. ■% of the patients in the MANDARA DB period discontinued the treatment and receive SoC. This was unusually low, and the clinical experts validated that it would be higher in a real-world setting in the UK. Moreover, the discontinuation rate of patients in the MANDARA OLE was ■%, much higher than the trial period data. In patients with severe asthma, benralizumab discontinuation rate was ■%. The company conservatively assumed a discontinuation rate ■% and explored a scenario with ■%. But the EAG thinks that there is significant uncertainty in the discontinuation rate.

OCS

The probability of OCS discontinuation was derived from MANDARA¹ based on the OCS dose of zero for the last 28 days of trial participation. It was applied in the model as ■%.⁵ The EAG is not aware of any evidence to suggest that the OCS discontinuation rate would continue beyond 1 year at the same rate indefinitely. It seems plausible that the benefit of benralizumab would be achieved within a short period of time after the start of treatment. It is possible that the highest rate of OCS discontinuation occurs within the first 6 months and the discontinuation rate falls to 0% by 1 year. This is explored in a scenario analysis where the OCS discontinuation rate is 0% after 1 year. In the EAG base case, the ■% annual discontinuation rate is modelled to decline linearly from 1 year to 0% at 5 years. While Figure 7 presents the change in average dose over time, rather than the rate of OCS discontinuation, if it is possible to infer change in rate of OCS discontinuation from average dose then it may suggest ■%

Figure 4.6: OCS usage by country across the 52-week trial period (full MANDARA population)



Source: Response to PFCs,¹⁶ Wechsler et al., 2024¹
Abbreviations: OCS = oral corticosteroids.

4.2.7.2 Treatment dose

The treatment dose of Benralizumab was 30mg Q4W and was informed the MANDARA trial. The dose for Soc (OCS and IS) were obtained from the Clinical Practice Research Datalink (CPRD) data, which is a 5-year database of inpatient and outpatient hospital episodes, patient care, accidents and emergencies in the UK. This was an excellent source of patient data and treatment regimen, and it is representative of the UK EGPA patient population. The source of information on acquisition costs of the treatment were obtained from BNF and eMIT. See Table 4.12Table .

Table 4.12: Treatment Acquisition Costs

Treatment	Unit		Per model cycle		Source
	Dose	Cost	Dose	Cost	
Benralizumab	30 mg	List price: £1,955 PAS price: [REDACTED]	1	List price: £1,955 PAS price: [REDACTED]	BNF ⁷⁵
OCS					
Prednisolone	5 mg	£0.41	1 mg	£0.00293	eMIT ⁶⁷
IS					
Azathioprine	50 mg	£1.20	[REDACTED] mg/day	£0.00043	eMIT ⁶⁷
Mycophenolate mofetil	500 mg	£6.55	[REDACTED] mg/day	£0.00026	eMIT ⁶⁷
Methotrexate	2.5 mg	£3.18	[REDACTED] mg/day	£0.01271	eMIT ⁶⁷
Source: CS Document B Section B.3.4.4, p.100 ⁵ Abbreviations: SE = standard error; CS = company submission; OCS = Oral Corticosteroids; IS = Immunosuppressants; BNF = British National Formulary; eMIT = Electronic Market Information Tool.					

4.2.7.3 EGPA state costs

The frequency of healthcare resource use was informed by the CRPD study, which considered patients with their first EGPA diagnosis code from 1 January 2006 and 28 February 2019, with at least 12 months of pre-diagnosis registration. The study was conducted in the UK clinical setting and was very comprehensive to cover most of the healthcare use by the patients. The NHS reference costs 2021-2022 and PSSRU 2023 were used to inform the unit costs of resource use. The unit costs were multiplied with the respective frequencies to obtain the health-state specific resource use costs per year in the model. See Table 4.13 and

Table 4.14

Table .

Table 4.13: Frequency of healthcare resource use, by health state, per patient per year for disease management

for disease management				
Resource	Mean			Source
	Remission	Stable disease	Relapse	
GP consultations	■	■	■	CPRD ⁸
Nurse consultations	■	■	■	
Outpatient visits	■	■	■	
ED visits	■	■	■	
Hospitalisations	■	■	■	
Critical care visits	■	■	■	
Source: CS Document B Table 59, Section B.3.5.2, p.105 ⁵ CPRD = Clinical Practice Research Datalink: ED = emergency department: GP = general practitioner				

Table 4.14: Unit Costs for Disease Management

Resource	Mean Unit Cost	Source
GP consultations	£49.00	PSSRU ⁶⁹
Nurse consultations	£8.83	
Outpatient visits	£188.08	National Cost Collection 2022-2023 ⁷⁶
ED visits	£262.68	
Hospitalisations	£1,217.53	
Critical care visits	£2,424.72	
Source: CS Document Table 60, B Section B.3.5.2, p.106 ⁵ Abbreviations: ED = emergency department; GP = general practitioner, PSSRU = Personal Social Services Research Unit		

4.2.7.4 OCS AE costs

The adverse effects of OCS treatment were modelled with the three most common chronic comorbidities as health states and adverse events as cycle of incidence with the effects spanning for a cycle length. The cost of adverse events was sourced from National Cost Collection 2022-23 and other literature sources which were the accepted and appropriate approach to model adverse events costs in the UK clinical setting.⁷⁶ But the adverse events associated with IS treatment was not modelled in the CS model. These AEs can have an impact on the adverse events costs incurred by the patient. So, the EAG has concerns over excluding these costs in the model.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results based on original model

The company's base-case cost-effectiveness results with PAS price presented in Table 65 in the CS.⁵ The deterministic base-case results which is presented in Table 5.1 Table shows that benralizumab provided an additional [REDACTED] QALYs per person at an incremental cost of [REDACTED] per person, resulting in an ICER of £25,314 per QALY gained. With a willingness-to-pay threshold of £30,000 per QALY, benralizumab is considered a cost-effective option, delivering a positive net health benefit (NHB) of 0.245 to the NHS (Table 5.6). The net monetary benefit of adding benralizumab as an odd on to the Soc versus SoC alone for a willingness to pay threshold of £30,000 was [REDACTED] (Table 5.3).

Table 5.1: Company base-case cost-effectiveness results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Benralizumab + SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£25,314
SoC (OCS + IS)	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-

Source: CS Document B, Table 65⁵
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants

Table 5.2: Company base-case results for net health benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£25,314	Not reported	0.245
SoC (OCS + IS)	[REDACTED]	-	-	-	-

Source: CS Document B, Table 65⁵
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

Table 5.3: Company base-case results for net monetary benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000	NMB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£25,314	[REDACTED]	[REDACTED]
SoC (OCS + IS)	[REDACTED]	-	-		

Source: CS Cost effectiveness model Excel file, deterministic results sheet⁷⁷
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

5.2 Company's sensitivity analyses

To explore uncertainty within their cost-effectiveness analysis, the company conducted deterministic and probabilistic sensitivity analyses. They also provided 5 probabilistic scenario analyses. The results are provided in sections 5.2.1, 5.2.2 and 5.2.3

5.2.1 Deterministic sensitivity analysis

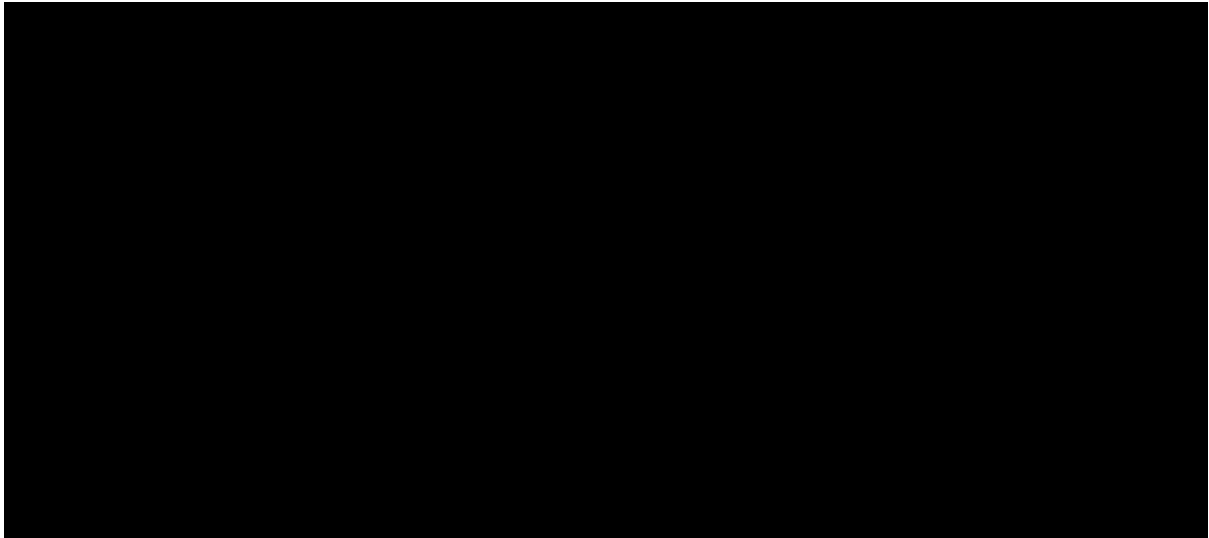
The company conducted a deterministic sensitivity analysis to assess the impact of individual inputs on the ICER associated with adding benralizumab to SoC compared to SoC. Parameters with known standard errors were varied within their 95% confidence intervals, while all other parameters were varied by $\pm 20\%$. and Figure 5.1 present the results of this analysis, highlighting the top 10 parameters with the with the greatest impact on the ICER. Health state utility (refractory) and the odds of achieving remission, derived from the Bucher ITC are the variables with the greatest impact on cost-effectiveness results. In this table, all parameters were varied within their 95% confidence intervals, except mortality and unit cost parameters which were varied by $\pm 20\%$.

Table 5.4 and Figure 5.1 present the results of this analysis, highlighting the top 10 parameters with the with the greatest impact on the ICER. Health state utility (refractory) and the odds of achieving remission, derived from the Bucher ITC are the variables with the greatest impact on cost-effectiveness results. In this table, all parameters were varied within their 95% confidence intervals, except mortality and unit cost parameters which were varied by $\pm 20\%$.

Table 5.4: Company's deterministic sensitivity analysis

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Health state utilities: Refractory			
ITC: OR for odds of remission			
Health state utilities: Remission			
Healthcare resource use: Remission			
Healthcare resource use: Stable disease			
Refractory disease: Risk reduction from baseline to week 52			
EGPA mortality: SMR for patients in remission			
OCS dosing: Daily dose of OCS for patients in stable disease			
Disease management costs: Unit costs			
Life tables: Background mortality			
Source: CS Cost effectiveness model Excel file, deterministic results sheet ⁷⁷ Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OR = odds ratio; PAS = patient access scheme; QALYs = quality-adjusted life years; SMR = standardised mortality ratio; SoC = standard of care.			

Figure 5.1: DSA tornado diagram for ICER for benralizumab versus SoC (with PAS)



Source: Source: CS Document B, Figure 19⁵

Abbreviations: DSA = deterministic sensitivity analysis; EGPA= eosinophilic granulomatosis with polyangiitis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OR = odds ratio; PAS = patient access scheme; QALYs = quality-adjusted life years; SMR = standardised mortality ratio; SoC = standard of care

5.2.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) with 1,000 iterations was conducted by the company to assess the simultaneous effect of uncertainty in the different model parameters and the robustness of the model to those variations.

The company's probabilistic sensitivity analysis provided in the Table 5.5 shows that adding benralizumab, as an add-on treatment to SoC, compared with SoC is associated with [REDACTED] QALY gained per person, with incremental cost of [REDACTED] resulting an ICER value of £26,310. The PSA results indicated that -at the willingness threshold value of £30,000 -benralizumab can be considered as a cost-effective option. Table 5.2 and Table 5.3 show the NHB and net monetary benefit (NMB) associated with benralizumab as 0.187 and [REDACTED] respectively.

Table 5.5: Company's probabilistic sensitivity analysis

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Benralizumab + SoC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£26,310
SoC (OCS + IS)	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-

Source: CS Document B, Table 66⁵
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

Table 5.6: Company's probabilistic sensitivity analysis results for net health benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£26,310	Not reported	0.187
SoC (OCS + IS)	[REDACTED]	-	-		

Source: CS Document B, Table 66⁵
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

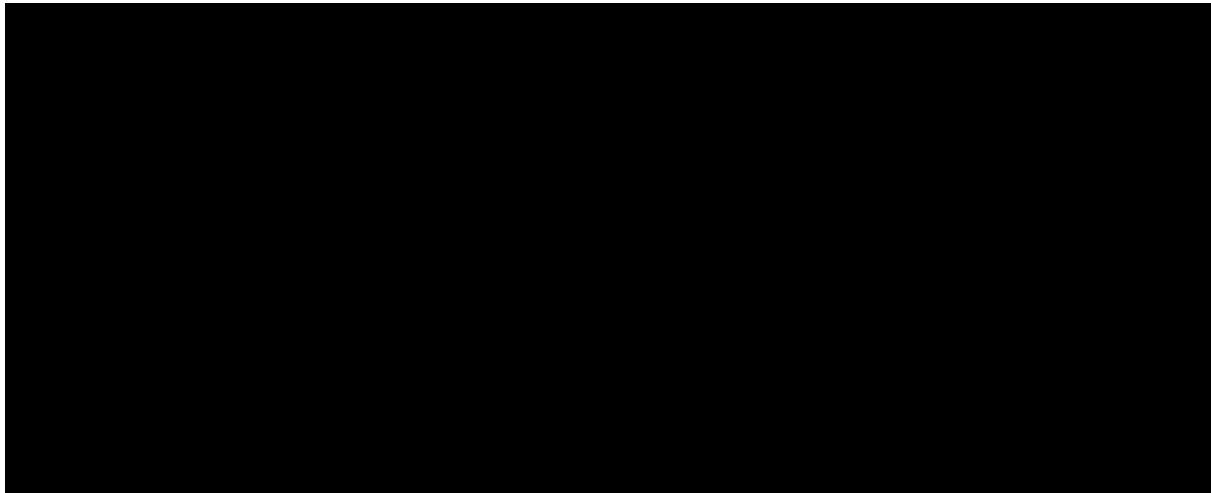
Table 5.7: Company's probabilistic sensitivity analysis results for net monetary benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000	NMB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£26,310	Not reported	[REDACTED]
SoC (OCS + IS)	[REDACTED]	-	-		

Source: CS Cost effectiveness model Excel file, PSA results sheet⁷⁷
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

The results of PSA are also provided in the CS in terms of ICER convergence plot, probabilistic cost-effectiveness plane and cost-effectiveness acceptability curve. (See [Figure 5.2](#), [Figure 5.3](#), and [Figure 5.4](#)).⁵ These analyses indicated that 1,000 iterations are sufficient, with a [REDACTED]% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY. Additionally, the cost-effectiveness acceptability curve indicates that this probability exceeds 50% at thresholds above ~£[REDACTED] per QALY.

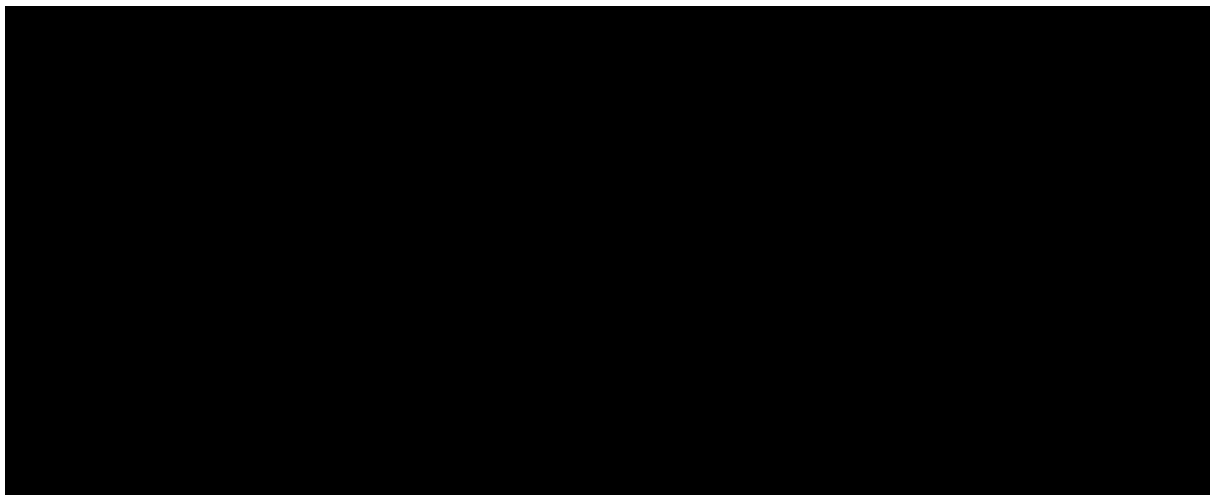
Figure 5.2 ICER convergence plot for benralizumab versus SoC (with PAS)



Source: CS Document B, Figure 16⁵

Abbreviations: ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PSA = probabilistic sensitivity analyses; QALYs = quality-adjusted life years; SoC = standard of care.

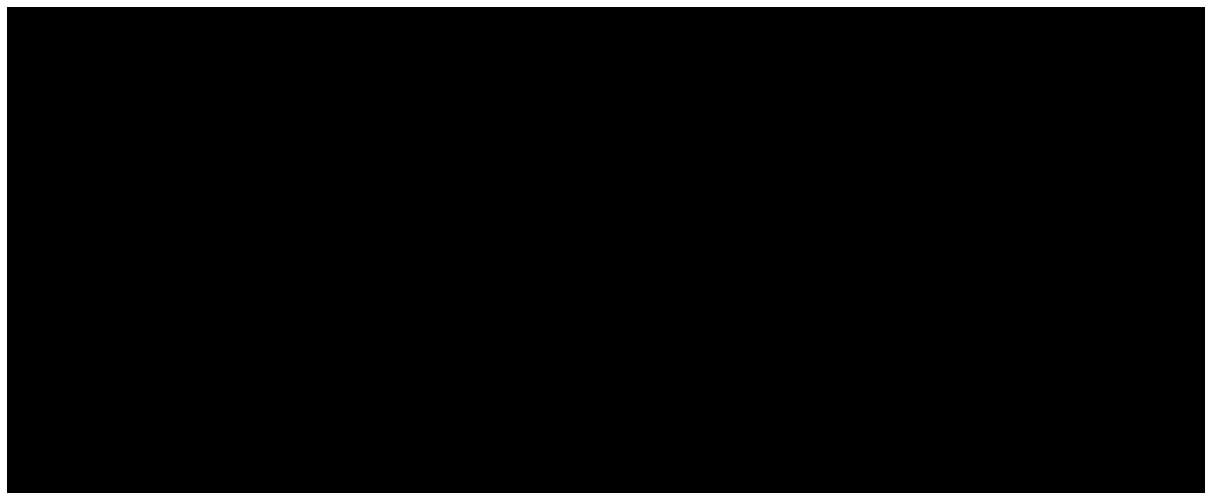
Figure 5.3 Probabilistic cost-effectiveness plane for benralizumab versus SoC (with PAS)



Source: CS Document B, Figure 17⁵

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analyses; QALYs = quality-adjusted life years; PAS: patient access scheme; SoC = standard of care

Figure 5.4 Cost-effectiveness acceptability curve for benralizumab versus SoC (with PAS)



Source: CS Document B, Figure 18⁵

Abbreviations: PAS = patient access scheme; SoC = standard of care

5.2.3 Scenario analysis

Five scenarios were conducted by the company and provided in the CS.⁵ Table 5.8 shows the details on each scenario and the result of analysis which indicated that adding benralizumab to SoC remained cost-effective compared to SoC at a willingness-to-pay threshold of £30,000/QALY.

EAG believe that the source of utility used in scenario analysis is not an appropriate source since the utility values for refractory state are extremely low.

Table 5.8: Probabilistic scenario analysis results for the company base-case

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
	Company base-case	N/A	N/A	██████	██	£26,310	0.19
1	Relative efficacy of benralizumab versus SoC	informed by the Bucher ITC • OR for remission: █████ • RR for ARR: █	informed by MAIC • OR for remission: █████ • RR for ARR: █	██████	██	£25,971	0.21
2	Health-state specific SMRs	informed by CPRD • Remission: █████ • Stable disease: █████ • Relapse: █	varied by +10%	██████	██	£26,700	0.17
			varied by -10%	██████	██	£25,846	0.21
3	Annual discontinuation rate for benralizumab	based on conservative midpoint of alternative sources • █%	midpoint of sources in Document B, ⁵ • █%	██████	██	£25,056	0.22
4	Proportion of patients in refractory sub-state, within stable	informed by MANDARA • Benralizumab arm: Starting % of █████%, then relative reduction	Reduction in Starting proportion by -5%	██████	██	£27,131	0.14

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental I QALYs	ICER (£)	Incremental NHB (£30,000)
	disease health state	applied) to yield █████% at week 52) informed by CPRD SoC arm: starting % of █████%, stayed constant	Increase in Starting proportion by +5%	█████	████	£25,556	0.23
5	Source of health state Utility	Adelphi DSP study ³	General population valuation from vignette study	█████	████	£16,049	1.16
			Patient valuation from vignette study	█████	████	£13,654	1.60

Source: CS Document B, Table 67⁵

Abbreviations: ARR = annualised relapse rate; CPRD = Clinical Practice Research Datalink; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NHB = net health benefit; OR = odds ratio; PAS = patient access scheme; QALY= quality-adjusted life year; RR = risk ratio; SMR = standardised mortality ratio; SoC = standard of care

5.3 Company's cost effectiveness results based on the updated model

The company updated the economic model in response to the EAG point on modelling responders for benralizumab after 1 year in clarification letter (question B11.a, Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON]).¹⁶ The results of the updated model are provided as follows:

5.3.1 Company's cost effectiveness results based on the updated model

The deterministic base-case results based on the updated model is presented in Table 5.9Table . There was a slight increase in the ICER value.

The base-case ICER was increased from £25,314 to £26,092 which with a willingness-to-pay threshold of £30,000 per QALY, benralizumab is still cost-effective option.

Table 5.9: Company base-case cost-effectiveness results (updated model)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£26,092
SoC (OCS + IS)	██████	██████	██████	-	-	-	-

Source: Updated Excel model submitted by the Company in response to points for clarification, question B11.a, deterministic results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

Table 5.10 and Table 5.11 show the show the result of analysis in the updated model as adding benralizumab as an add on to SoC versus SoC alone, with WTP threshold of £30,000, delivered NHB and NMB equal to 0.198 and ██████, respectively.

Table 5.10: Company base-case results for net health benefit (updated model)

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
Benralizumab + SoC	██████	██████	£26,092	Not reported	0.198
SoC (OCS + IS)	██████	-	-		

Source: Updated Excel model submitted by the Company in response to points for clarification, question B11.a, deterministic results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

Table 5.11: Company base-case results for net monetary benefit (updated model)

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000	NMB at £30,000
Benralizumab + SoC	██████	██████	£26,092	██████	██████

SoC (OCS + IS)		-	-		
Source: CS updated Excel model submitted by the Company in response to points for clarification, question B11.a, deterministic results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON]) ¹⁶ Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroids; SoC = standard of care; IS = immunosuppressants.					

The cost and QALY breakdown in the CS model (Table 5.12 and Table 5.13) help to indicate the drivers of the model: the effect of benralizumab on increasing the number of patients in remission and reducing the number of refractory patients, and the drug acquisition cost.

Table 5.12: Breakdown of cost in company base-case result (updated model)

Component	Benralizumab + SoC	SoC	Incremental
Remission			
Non-refractory disease			
Refractory disease			
Relapse			
Drug acquisition			
OCS comorbidity management			
Total			
Source: CS updated model Excel file [REDACTED] deterministic results sheet ¹⁶ Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.			

Table 5.13: Breakdown of QALY in company base-case result

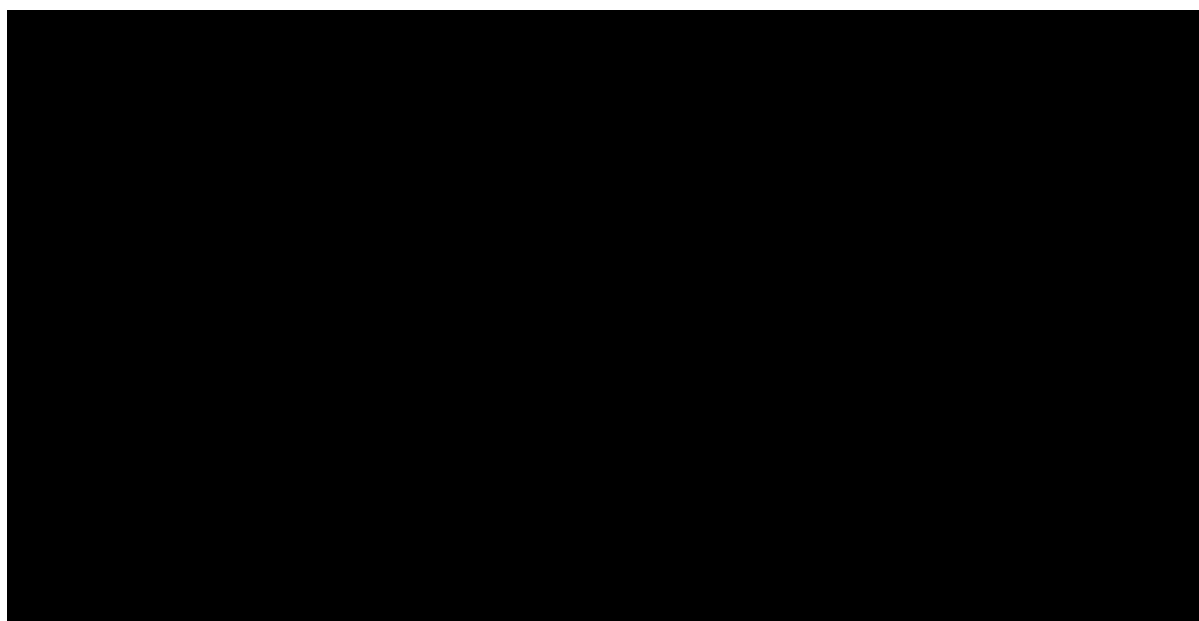
Component	Benralizumab + SoC	SoC	Incremental
Remission			
Non-refractory disease			
Refractory disease			
Relapse			
OCS-related comorbidities			
Total			
Source: CS updated model Excel file [REDACTED] deterministic results sheet ¹⁶ Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.			

5.4 Company's sensitivity analyses based on the updated model

5.4.1 Deterministic sensitivity analysis

Figure shows the results of deterministic sensitivity analysis in the updated model in terms of tornado diagram. Refractory health state utility, remission odds ratio and remission health state utility were the three variables with greatest impact on the ICER.

Figure 5.5: DSA tornado diagram for ICER for benralizumab versus SoC with PAS (updated model)



Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶

Abbreviations: DSA = deterministic sensitivity analysis; EGPA = eosinophilic granulomatosis with polyangiitis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OR = odds ratio; PAS = patient access scheme; QALYs = quality-adjusted life years; SMR = standardised mortality ratio; SoC = standard of care.

5.4.2 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis based on the updated model is provided in the Table 5.14 It shows that adding benralizumab, as an add-on treatment to SoC in compared with SoC is associated with ■■■ QALY gained per person, with incremental cost of ■■■ resulting an ICER value of £27,166.

The PSA results indicated that -at the willingness threshold value of £30,000 – adding Benralizumab to SoC can be considered as a cost-effective option.

Table 5.14: Company's probabilistic sensitivity analysis

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Benralizumab + SoC	■■■	■■■	■■■	■■■	■■■	■■■	£27,166
SoC (OCS + IS)	■■■	■■■	■■■	-	-	-	-

Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; OCS = oral corticosteroid; SoC = standard of care; IS = immunosuppressants.

The NHB and NMB associated with benralizumab were as 0.139 and [REDACTED] respectively. (See Table 5.6 Table and Table 5.7).

Table 5.15: Company's probabilistic sensitivity analysis results for net health benefit (updated model)

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£27,166	Not reported	0.139
SoC (OCS + IS)	[REDACTED]				

Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; OCS = oral corticosteroids; SoC = standard of care; IS = immunosuppressants.

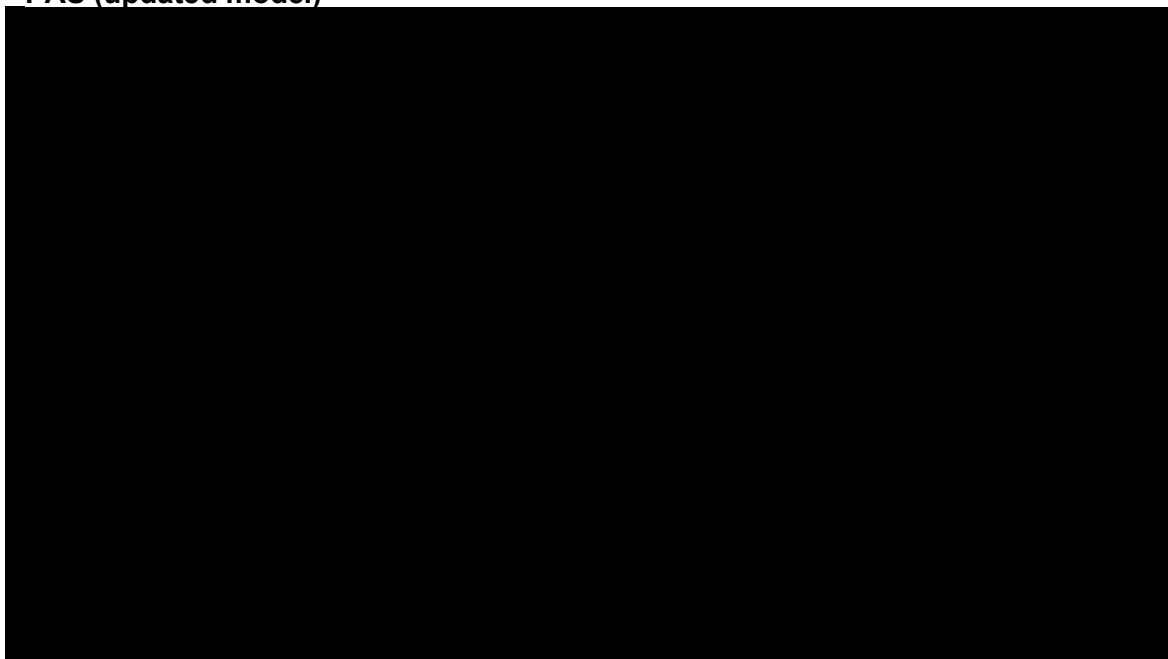
Table 5.16: Company's probabilistic sensitivity analysis results for net monetary benefit (updated model)

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000	NMB at £30,000
Benralizumab + SoC	[REDACTED]	[REDACTED]	£27,166	[REDACTED]	[REDACTED]
SoC (OCS + IS)	[REDACTED]				

Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
 Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroids; SoC = standard of care; IS = immunosuppressants.

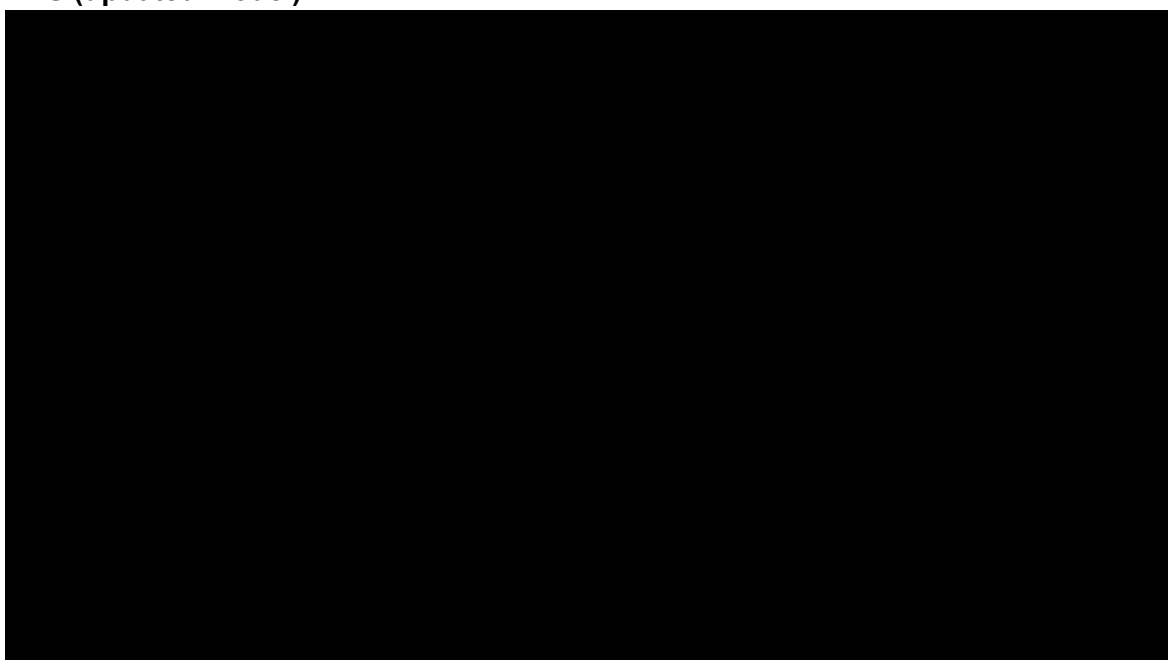
In the updated model, probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY decreased from 70.1% to 66.5%. (Figure and Figure)

Figure 5.6: Probabilistic cost-effectiveness plane for benralizumab versus SoC with PAS (updated model)



Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
Abbreviations: ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PSA = probabilistic sensitivity analyses; QALYs = quality-adjusted life years

Figure 5.7: Cost-effectiveness acceptability curve for benralizumab versus SoC with PAS (updated model)



Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON])¹⁶
Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PSA: probabilistic sensitivity analyses; QALYs: quality-adjusted life years.

Table 5.17 Deterministic scenario analysis results for the company base-case (updated model)

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
	Company base-case	N/A	N/A	████████	████	£26,092	0.198
1	Relative efficacy of benralizumab versus SoC	informed by the Bucher ITC • OR for remission: █████ • RR for ARR: █████	informed by MAIC • OR for remission: █████ • RR for ARR: █████	████████	████	£25,646	0.223
2	Health-state specific SMRs	informed by CPRD • Remission: █████ • Stable disease: █████ • Relapse: █████	varied by +10%	████████	████	£26,509	0.175
			varied by -10%	████████	████	£25,598	0.226
3	Annual discontinuation rate for benralizumab	based on conservative midpoint of alternative sources • █%	midpoint of sources in Document B, ⁵ • █%	████████	████	£24,877	0.227
4	Proportion of patients in refractory sub-state, within stable	informed by MANDARA • Benralizumab arm: Starting % of █████%, then relative reduction	Reduction in Starting proportion by -5%	████████	████	£26,898	0.152

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
	disease health state	applied) to yield █% at week 52) informed by CPRD SoC arm: starting % of █%, stayed constant	Increase in Starting proportion by +5%	█	█	£25,351	0.242
5	Source of health state Utility	Adelphi DSP study ³	General population valuation from vignette study	█	█	£15,975	1.160
			Patient valuation from vignette study	█	█	£13,603	1.592
Source: CS updated Excel model, submitted by the Company in response to points for clarification, question B11.a, DSA Results sheet (Benralizumab in EGPA Cost effectiveness model_17Jan25_[CON]) ¹⁶ Abbreviations: ARR = annualised relapse rate; CPRD = Clinical Practice Research Datalink; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NHB = net health benefit; OR = odds ratio; PAS = patient access scheme; QALY= quality-adjusted life year; RR = risk ratio; SMR = standardised mortality ratio; SoC = standard of care							

5.5 Model validation and face validity check

For internal validity, economic model structure, inputs and assumptions were validated by the company through obtaining feedback from clinical experts⁹ and health economic experts in the UK.⁷⁰

5.5.1 Face validity assessment and technical verification

The face validity and the technical verification of the model was found to be satisfactory by the EAG.

5.5.2 Comparison with external data

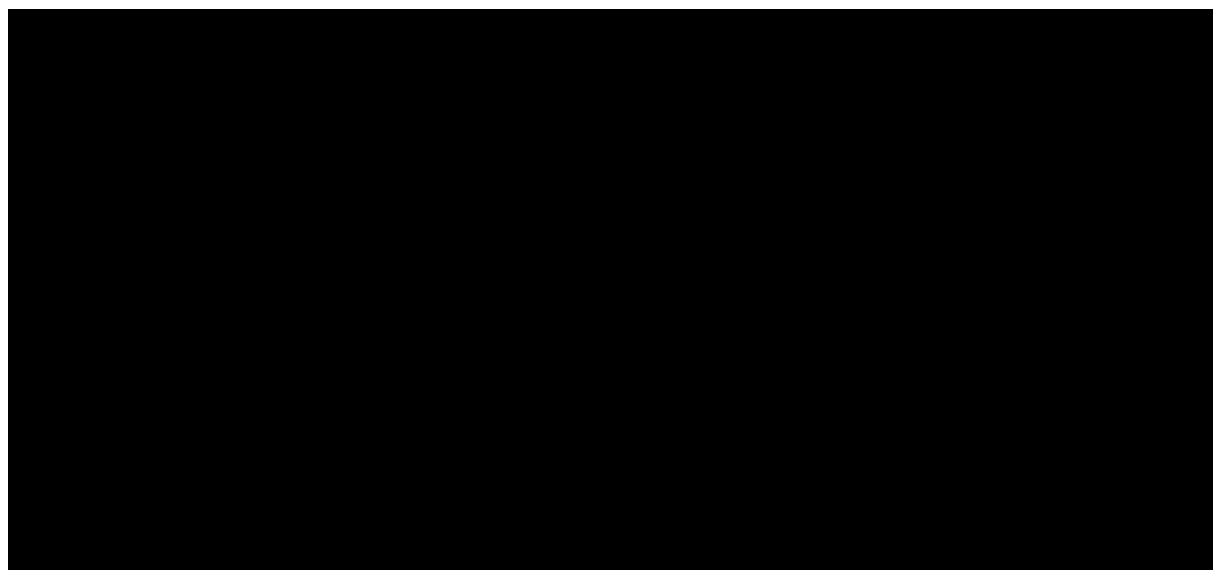
The EAG noted that the company discussed the internal validity of the economic model within the external validity section. Therefore, the company was requested to present comparisons of model predictions at appropriate time points for survival, OCS chronic and acute conditions, and the percentages in each EGPA state (either from the starting cohort or among surviving patients) based on published and available evidence.

The EAG acknowledges the limited evidence related to EGPA and, in the absence of external patient data for model validation, has asked the company to provide clinical expert opinions on the validity of these predictions.

In response to the clarification letter, the company provided more detail on how the company validated the model prediction in the absence of external patient data. They provided model predictions for the requested outcomes by treatment arm over the model's time horizon as shown below.¹⁶

It is also indicated that Clinical experts found the model outputs in line with their expectations for a non-severe EGPA population.

Figure 5.8 Model prediction of survival by treatment arm



Source: CS clarification letter¹⁶
Abbreviations: SoC: standard of care

**Figure 5.10: Model prediction of OCS-related chronic events,
SoC arm**

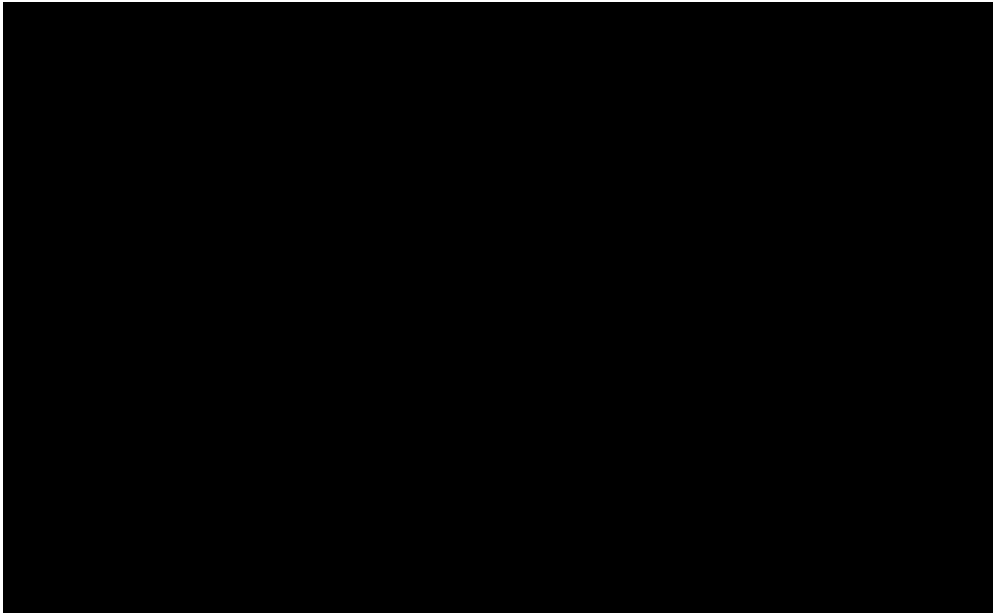
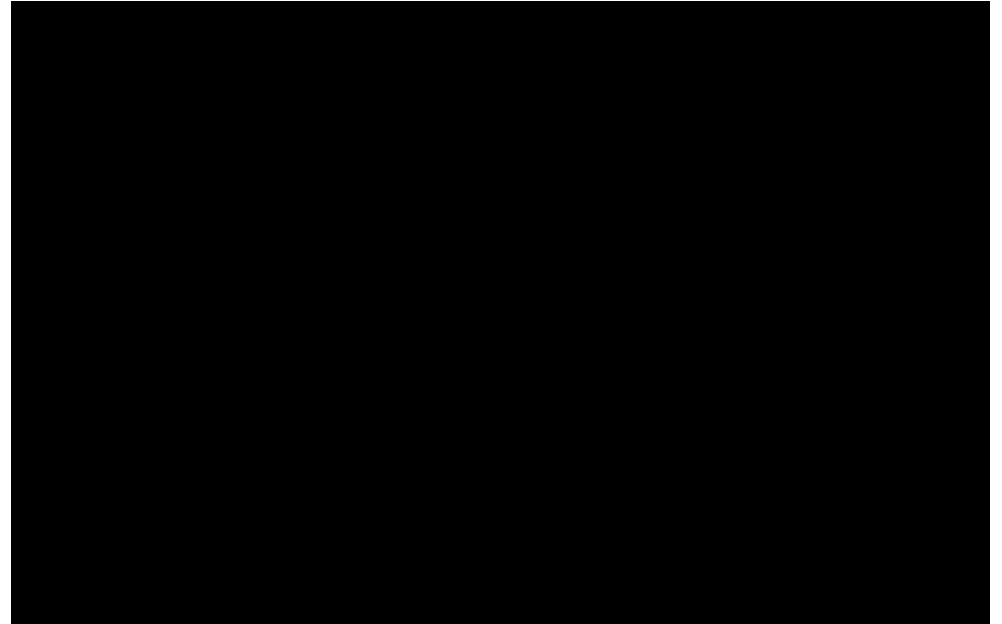


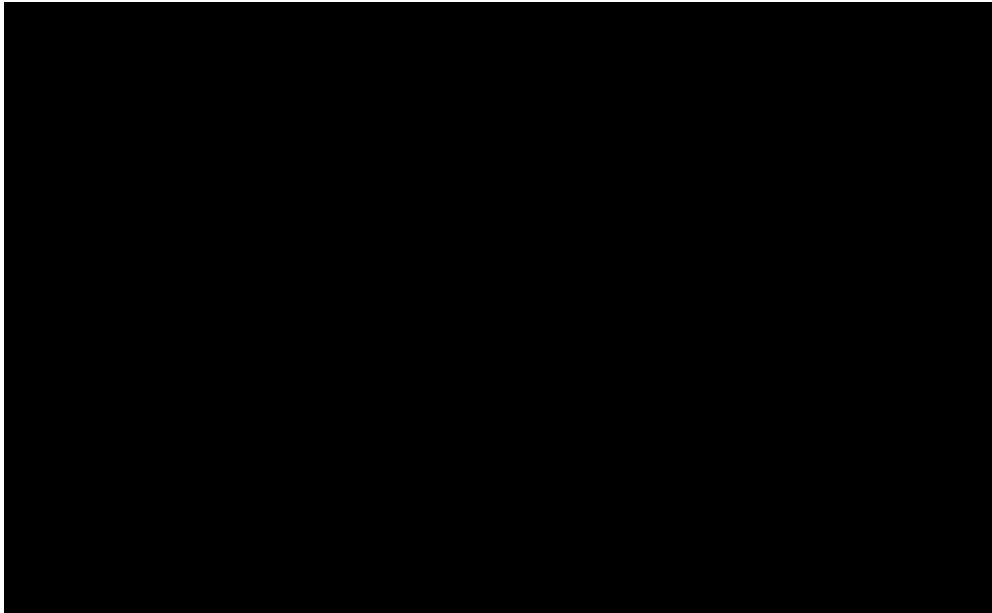
**Figure 5.9: Model prediction of OCS-related chronic events,
benralizumab arm**



Source: Source: CS clarification letter ¹⁶

Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroids; SoC = standard of care; T2DM = Type-2 diabetes mellitus

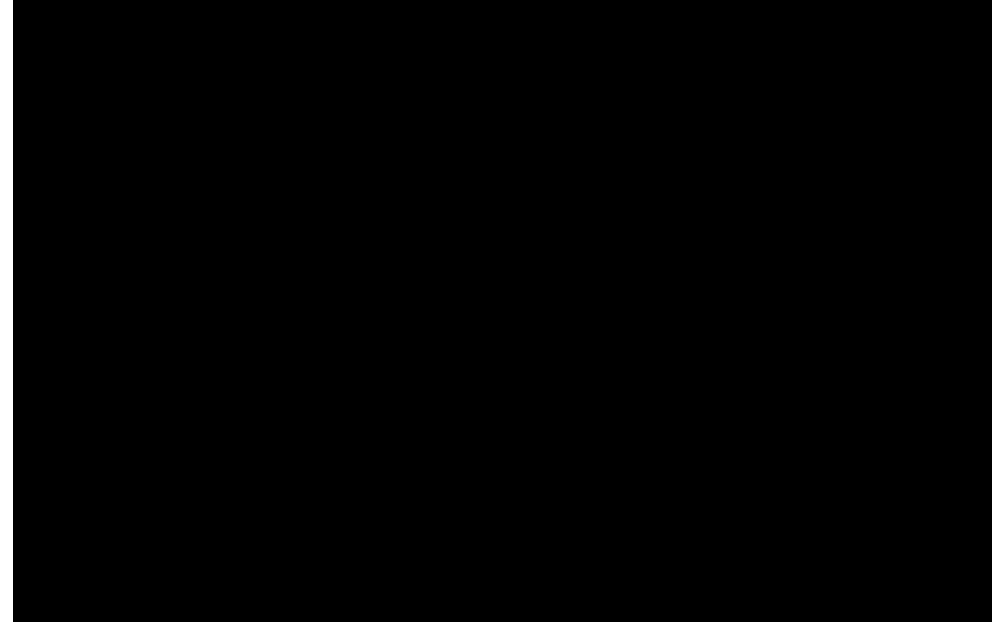
Figure 5.12: Model prediction of OCS-related acute events, SoC arm



Source: CS clarification letter¹⁶

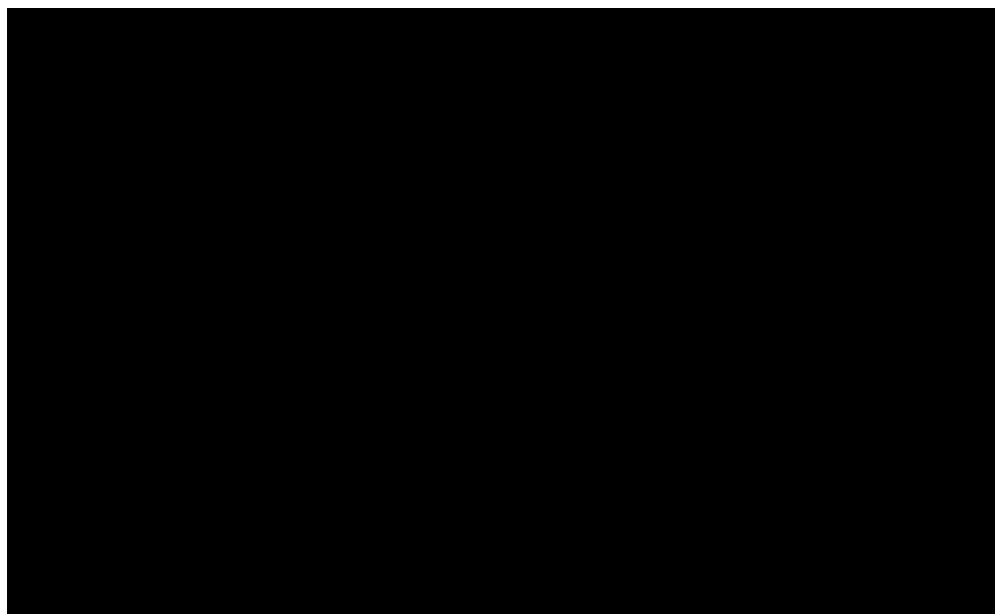
Abbreviations: OCS: oral corticosteroids; SoC: standard of care
Abbreviations: OCS: oral corticosteroids; SoC: standard of care

Figure 5.11: Model prediction of OCS-related acute events, benralizumab arm



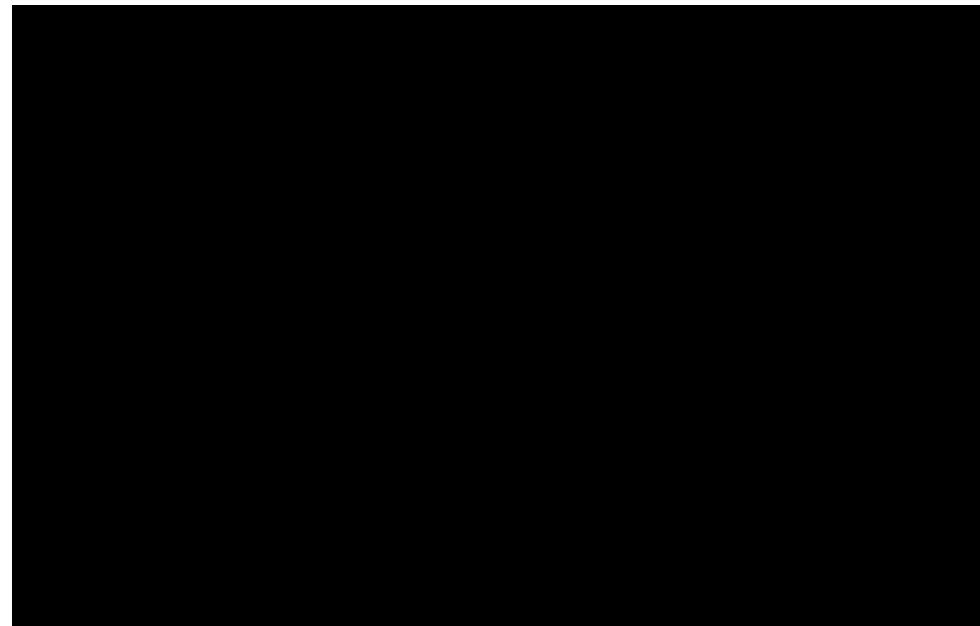
Source: CS ¹⁶

Figure 5.14: Model prediction of health state occupancy; SoC arm



Source: CS clarification letter¹⁶

Figure 5.13: Model prediction of health state occupancy; benralizumab arm



Source: CS ¹⁶

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 *Exploratory and sensitivity analyses undertaken by the EAG*

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included two main adjustments to the company base-case presented in Section 6.1.1. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016).⁷⁸

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG Base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

No errors were identified that required fixing.

Fixing violations

No violations to the NICE reference case were identified by the EAG.

Matters of judgement

See the Appendix for descriptions to changes to the model for the EAG analyses.

6.1.1.1 *Increased utility for the refractory and relapse states*

The EAG made the assumption that those in the refractory and relapse states are more likely to have organ damage than those in the non-refractory and remission states, the EAG increased the utility in the refractory and relapse states by ■■■, the average disutility across all of the acute and chronic events. It makes the simplifying assumption that everyone in refractory and relapse states in the Adelphi DSP study has one and only one acute or chronic OCS event in equal numbers, and that no-one in the remission and non-refractory states in the Adelphi DSP study has an acute or chronic OCS event.³ See Section 4.2.6. This is a simple assumption based on very little evidence. It is possible that only the refractory state is at significant risk of utility underestimation relative to other states. Ideally, more evidence would be available to inform utility adjustments across states. See Scenario 14 where only the utility for the refractory state is increased by ■■■, and the utility for relapse remains as it is in the CS model.

6.1.1.2 *Linear decline in the OCS discontinuation rate from 1 year*

The OCS discontinuation rate in the benralizumab arm was assumed to be ■■■% per year. The EAG considers it quite possible that the OCS discontinuation rate will decline over time. In the

EAG base case the discontinuation rate is assumed to decline linearly from ■% at year 1 to 0% at year 5. See Section 0.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case. As well as replicating the company scenario analysis on the EAG base case. The EAG conducted some additional analyses (EAG Exploratory Scenario Analysis

Table 6.11 shows the results of EAG exploratory scenario analysis on the EAG-base case. Scenario 6, 12 and 13 have the highest impact on ICER with values £33,338, £34,006, £33,157, respectively.

Table 6.11), detailed below.

6.1.2.1 Mortality

In the CS model, the mortality effect of EGPA was incorporated by including mortality hazard ratios for remission (1.5), stable (2.27) and relapse (3.33) states versus the general population mortality. The EAG was interested to explore the impact of incorporating OCS chronic event mortality hazard ratios in the model. As the risk of OCS chronic events increases over time, the expectation is that hazard ratios versus the general population may increase over time.

The risk of OCS acute and chronic events in the CS model was modelled based on the evidence from Gibson et al (2024).⁷ The same publication reported HRs for the chronic events versus the absence of the chronic events. The Gibson et al. (2024)⁷ mortality HRs are presented in Table 6.1. There are two common ways of implementing HRs: (1) multiplying HRs together (Scenario 1), and (2) assuming that event HRs are the same or similar regardless of whether or not a person has EGPA (Scenario 2). The EAG thinks Scenario 2 is more likely.

Table 6.1: Morality hazard ratios vs EGPA/no event

Event	Gibson et al, 2024 ⁷
	vs no event
T2DM	2.07
eCVD	1.28
OP	1.36
T2DM/eCVD	2.07
T2DM/OP	8.50
eCVD/OP	1.36
T2DM/eCVD/OP	8.50
Source: EAG base-case Excel Model Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroid; OP = Osteoporosis; EGPA = eosinophilic granulomatosis with polyangiitis; T2DM = type 2 diabetes mellitus	

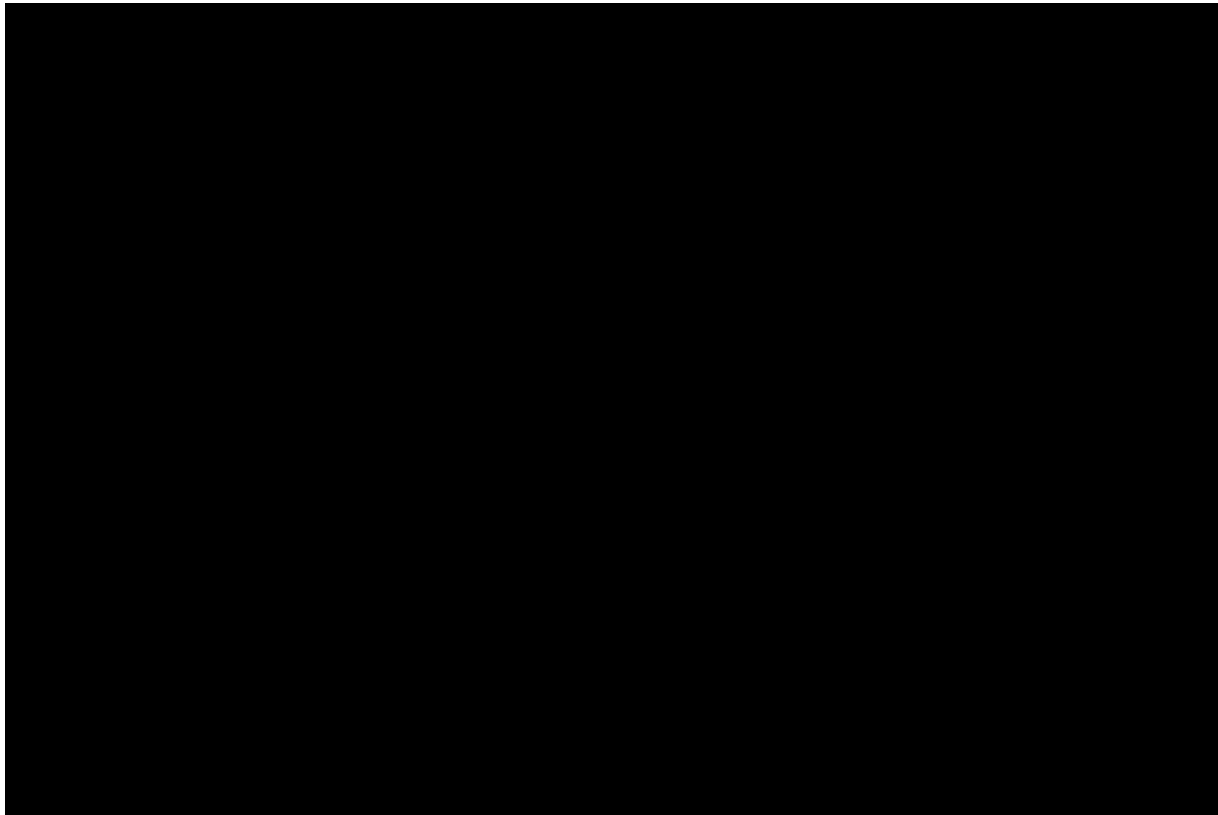
Table 6.2: Hazard ratios versus the general population

Health State	Event	EAG Survival A (Scenario 1)	EAG Survival B (Scenario 2)
		vs gen pop	vs gen pop
Remission	Event free	1.01	1.01
	T2DM	3.11	2.16
	eCVD	1.92	1.70
	OP	2.04	1.75
	T2DM/eCVD	3.11	2.16
	T2DM/OP	12.75	4.37
	eCVD/OP	2.04	1.75
	T2DM/eCVD/OP	12.75	4.37
Stable	Event free	1.52	1.52
	T2DM	4.70	3.27
	eCVD	2.91	2.57
	OP	3.09	2.65
	T2DM/eCVD	4.70	3.27
	T2DM/OP	19.30	6.62
	eCVD/OP	3.09	2.65
	T2DM/eCVD/OP	19.30	6.62
Relapse	Event free	2.23	2.23
	T2DM	6.89	4.79
	eCVD	4.27	3.77
	OP	4.53	3.88
	T2DM/eCVD	6.89	4.79
	T2DM/OP	28.31	9.71
	eCVD/OP	4.53	3.88
	T2DM/eCVD/OP	28.31	9.71
Source: EAG base-case Excel Model Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroid; OP = Osteoporosis; EGPA = eosinophilic granulomatosis with polyangiitis; T2DM = type 2 diabetes mellitus			

- Additional Scenario 1 – Inclusion of OCS chronic event mortality hazard ratios A

In EAG Scenario 1, the OCS event mortality HRs are multiplied by the EGPA state mortality ratios. The HRs of the events by EGPA state of the event versus the general population are presented in Table 6.2.

Figure 6.1 The proportion of patients alive over time for benralizumab and SoC (Scenario 1)



Source: EAG base-case Excel Model

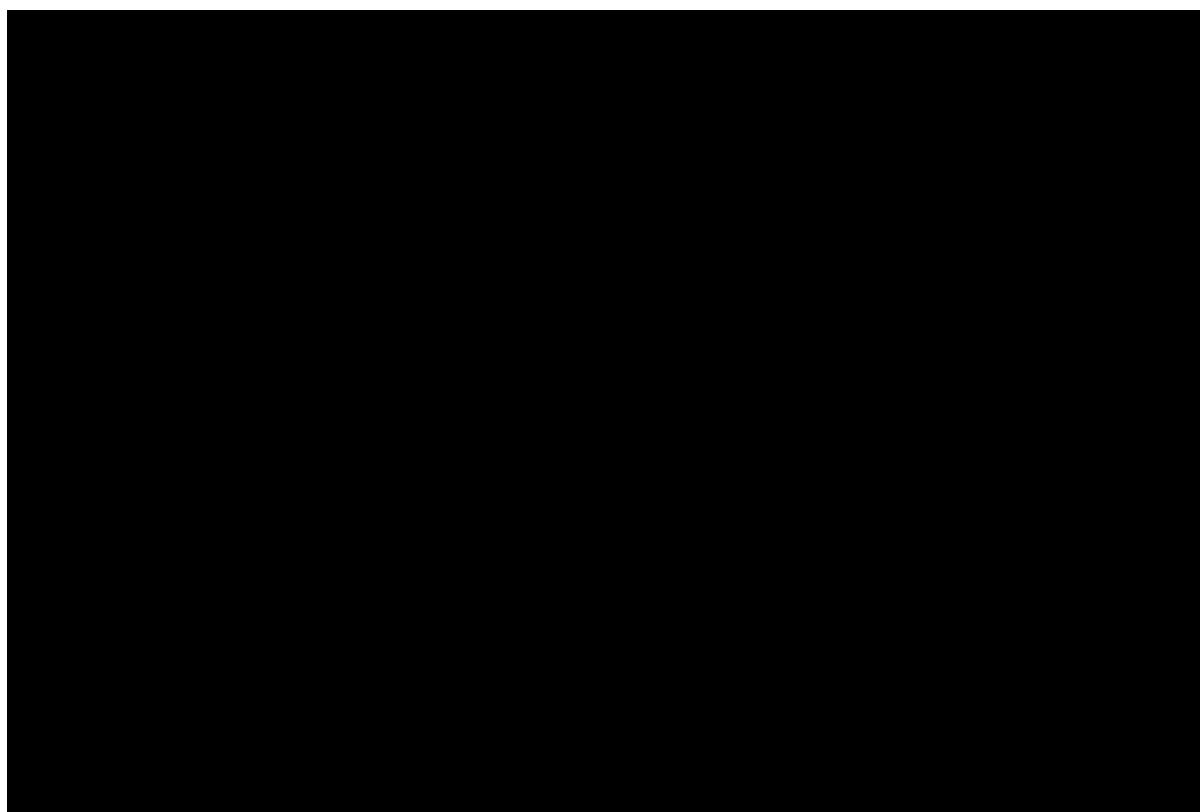
Abbreviations: CS = company submission; [REDACTED]

- Additional Scenario 2 – Inclusion of OCS chronic event mortality hazard ratios B

As it mentioned above, there are two common ways of implementing HRs: (1) multiplying HRs together, and (2) assuming that event HRs are the same or similar regardless of whether or not a person has EGPA.

In EAG Scenario 2, the OCS event mortality HR for T2DM is calibrated to be just slightly higher than the Gibson et al. (2024) mortality HR for T2DM.⁷ The mortality HRs for the stable and relapse states are correspondingly higher. The event free mortality HR for the remission state was calibrated to be roughly 1.

Figure 6.2 The proportion of patients alive over time for benralizumab and SoC (Scenario 2)



Source: EAG base-case Excel Model

Abbreviations: CS = company submission; SoC = standard of care

6.1.2.2 OCS discontinuation and second-line SoC effectiveness

The company model makes the following related assumptions with associated consequences:

Assumptions

- (1) Patients who discontinue OCS in the benralizumab arm never restart OCS after discontinuing benralizumab. This leads to a much lower percentage of patients receiving OCS as part of SoC.
- (2) The proportion of responders is the same for those who do not discontinue OCS while on benralizumab and those who do discontinue OCS while on benralizumab. The benralizumab discontinuation rate is the same for those who do and those who do not discontinue OCS.

A consequence of these assumptions is:

- The percentage of patients receiving SoC after benralizumab discontinuation who received OCS is continually decreasing.

This leads to the following assumption implicit in the CS model:

- (3) The relative risk of SoC with OCS vs SoC without OCS = 1. The transition probabilities for SoC are the same regardless of the percentage of patients receiving OCS.

The assumptions (1), (2) and (3) contribute to the following consequence:

- The greater the rate of benralizumab discontinuation, the lower the ICER for benralizumab. This is because SoC after benralizumab dominates SoC (greater QALYs and lower cost). The effectiveness is the same and the lower OCS use results in lower OCS acute and chronic events and thus greater QALYs and lower costs.

The following assumptions are also made:

- (4) The percentage of stable patients who are refractory is ■■■% with SoC after benralizumab discontinuation, which is the same as in the SoC arm of the model.
- (5) The OCS discontinuation rate is constant after 1 year.
- (6) The benralizumab discontinuation rate is constant.

The EAG believes that OCS is considered important treatment as part of SoC. It likely has an effect on remission, stable and relapse states. The EAG explores alternatives to assumptions (1), (2) and (3) in Scenarios 3-7. Scenarios 3-5 explore different relative risks of improvement in EGPA state for SoC with OCS versus SoC without OCS. Scenario 6 explores removing assumption (2). Scenario 7 explores removing assumption (1).

- Additional Scenario 3 – RR of SoC with OCS vs SOC without OCS = 2

The EAG does not have any evidence for the relative risk of improving EGPA state for SoC with OCS vs SoC without OCS. This scenario assumes a relative risk of improving the EGPA health state (e.g. from stable to remission, relapse to stable) of 2. The predicted percentage of patients receiving SoC in each EGPA state at different time points is presented in Table 6.3. The associated transition probabilities are reported in Table 6.4.

Table 6.3 Proportion of patients in EGPA health states while receiving SoC in the benralizumab arm at different time points

Scenario/ health state/ Time	EAG base case			Scenario 3			Scenario 4			Scenario 5		
	Remission	Stable disease	Relapse	Remission	Stable disease	Relapse	Remission	Stable disease	Relapse	Remission	Stable disease	Relapse
Year 1	5.19%	86.00%	8.81%	5.02%	85.97%	9.01%	4.92%	85.94%	9.15%	4.86%	85.91%	9.23%
Year 5	14.95%	75.97%	9.08%	10.81%	75.25%	13.94%	8.63%	73.11%	18.26%	7.52%	71.18%	21.30%
Year 10	13.55%	77.26%	9.19%	8.91%	76.02%	15.07%	6.60%	72.69%	20.71%	5.48%	69.67%	24.85%

Source: EAG model

Table 6.4 Transition probabilities for SoC after discontinuation of benralizumab

Transitions	EAG base case	OCS SoC vs no OCS SoC Hazard Ratio		
		2	4	8
Remission -> Remission	0.93	0.86	0.72	0.44
Remission -> Stable disease	0.04	0.08	0.17	0.34
Remission -> Relapse	0.03	0.06	0.11	0.22
Stable disease -> Remission	0.01	0.00	0.00	0.00
Stable disease -> Stable disease	0.91	0.83	0.67	0.34
Stable disease -> Relapse	0.08	0.17	0.33	0.66
Relapse -> Remission	0.01	0.01	0.02	0.05
Relapse -> Stable disease	0.73	0.36	0.18	0.09
Relapse -> Relapse	0.27	0.63	0.80	0.86
Source: EAG model				

- Additional Scenario 4 – RR of SoC with OCS vs SOC without OCS = 4

The EAG does not have any evidence for the relative risk of improving EGPA state for SoC with OCS vs SoC without OCS. This scenario assumes a relative risk of improving the EGPA health state (e.g. from stable to remission, relapse to stable) of 4. The predicted percentage of patients receiving SoC in each EGPA state at different time points is presented in Table 6.3. The associated transition probabilities are reported in Table 6.4.

- Additional Scenario 5 – RR of SoC with OCS vs SOC without OCS = 8

The EAG does not have any evidence for the relative risk of improving EGPA state for SoC with OCS vs SoC without OCS. This scenario assumes a relative risk of improving the EGPA health state (e.g. from stable to remission, relapse to stable) of 8. The predicted percentage of patients receiving SoC in each EGPA state at different time points is presented in Table 6.3. The associated transition probabilities are reported in Table 6.4.

- Additional Scenario 6 – Those who discontinue OCS do not discontinue benralizumab

The company made the following assumption (from those listed above):

- (2) The proportion of responders is the same for those who do not discontinue OCS while on benralizumab and those who do discontinue OCS while on benralizumab.

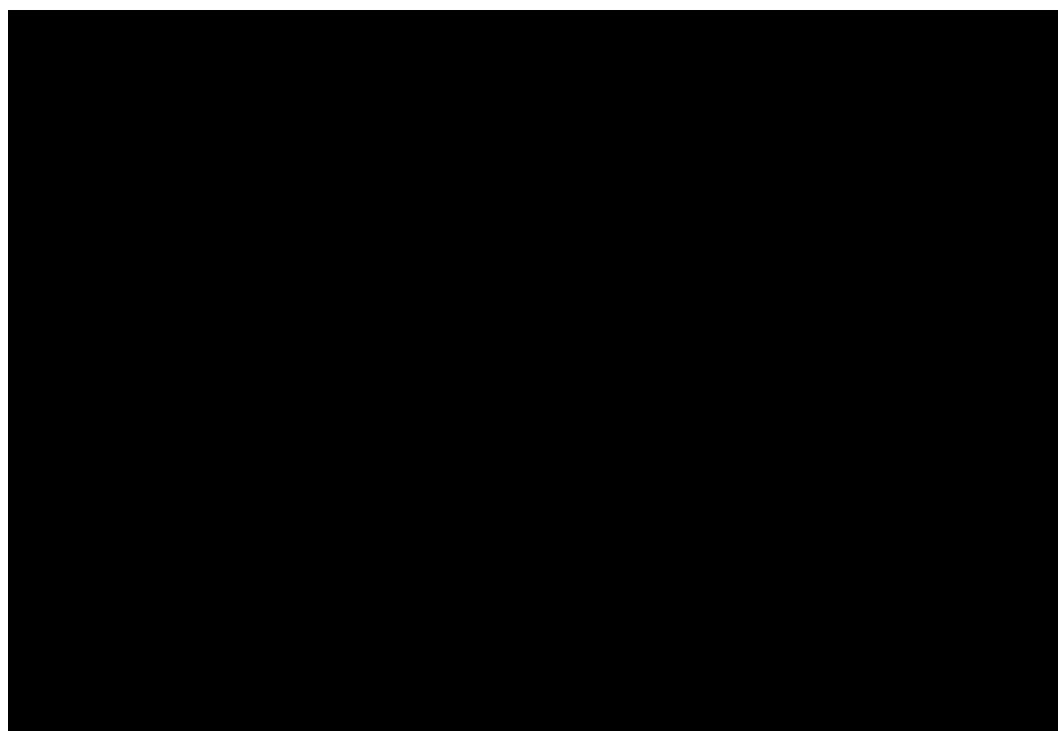
This Scenario (6) assumes that patients who discontinue OCS while on benralizumab do so because they are responders and they do not subsequently discontinue benralizumab.

The proportion of patients receiving SoC after benralizumab discontinuation who receive OCS over time is presented in Figure 6.3. It does not remain constant because the percentage of patients who receive OCS and continue to receive OCS when they discontinue benralizumab is <100%, while 100% of those who never started OCS still do not receive OCS when they discontinue benralizumab.

The percentage of SoC who receive OCS is higher in the EAG base case than the company base case because the EAG base case assumes that the discontinuation rate of OCS declines linearly over 4 years from year 1 rather than remain constant over the model time horizon.

Another consequence of the OCS assumption in this scenario is that the benralizumab discontinuation rate only applies to those patients still taking OCS. The discontinuation rate is therefore calibrated so that (1) the percentage who have discontinued benralizumab at 12 months is roughly █% and the percentage who have discontinued OCS at 12 months is █% and the response at 12 months is 65%. While the model is calibrated to achieve a high benralizumab discontinuation rate in those who do not discontinue OCS, there is a cap on the total who discontinue amongst those who are alive. The numbers on benralizumab in the EAG base case and in this scenario are presented in Figure 6.4.

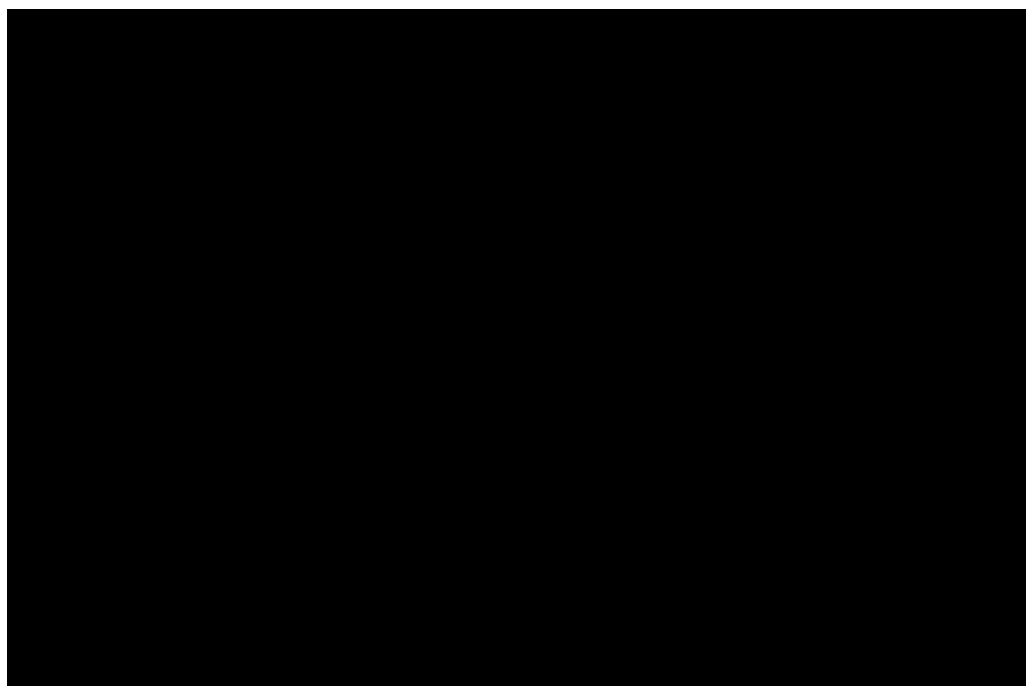
Figure 6.3: The proportion of patients receiving SoC who receive OCS (after benralizumab discontinuation)



Source: EAG model

Abbreviations: CS = company submission; SoC = standard of care; OCS = oral corticosteroids

Figure 6.4: The model prediction for the number of patients receiving benralizumab



Source: EAG model

- Additional Scenario 7 – Those who discontinue OCS restart OCS after discontinuing benralizumab

The company made the following assumption (from those listed above):

- (1) Patients who discontinue OCS in the benralizumab arm never restart OCS, even after discontinuing benralizumab. This leads to a much lower % receiving OCS on SoC.

This Scenario (7) assumes that patients who discontinue OCS while on benralizumab restart OCS if they subsequently discontinue benralizumab. This ensures that the percentage of patients receiving SoC after benralizumab discontinuation remains constant at the same level as for the SoC arm of the model. This is shown in Figure 6.3.

- Additional Scenario 8 - OCS discontinuation rate drops to 0% after 12 months

The company had assumed a continuous discontinuation rate for OCS in patients in the benralizumab arm. The assumption made in the EAG base-case is that there was a linear reduction in the OCS discontinuation. The OCS discontinuation is based on improvement in symptoms and odds of achieving remission in the patients and it can differ from patient to patient. Since individualised patient data was not captured in the model, EAG conducted a scenario analysis where the OCS discontinuation rate in the benralizumab patient arm dropped to 0. This helps to understand the effect of OCS discontinuation rates in the cost-effectiveness of benralizumab + SoC in treatment of EGPA.

- Additional Scenario 9: OCS discontinuation rate is constant for the duration of the model

There was a linear reduction in the OCS discontinuation rate to 0 from year 1 to year 5 implemented in the EAG base-case. In scenario 9, this assumption was removed to obtain a constant discontinuation rate for OCS in patients in the benralizumab + OCS arm of treatment. A constant discontinuation rate of █% was included for the patients receiving benralizumab + OCS over the period of model length, which was assumed in the company-base case as well.

6.1.2.3 Benralizumab discontinuation rate

- Scenario 10: Benralizumab discontinuation rate of █%

Due to lack of evidence in benralizumab discontinuation rate, EAG considered exploratory scenario analyses using discontinuation rates informed by various source. In this scenario 10, the discontinuation rate observed in the MANDARA DB trial █% explored by EAG.

- Scenario 11: Benralizumab discontinuation rate of █%

In scenario 11, the EAG modelled a scenario with the benralizumab discontinuation rate of █%, which was informed by MANDARA OLE trial. This helped EAG to explore a scenario in which the Benralizumab discontinuation rate is higher than what the company had considered in their submission.

- Scenario 12: combination of scenarios 6 & 10

The scenario 12 is a combination of scenarios 6 and 10. In this scenario, a patient who discontinue OCS in the benralizumab arm do not discontinue benralizumab and the discontinuation rate of benralizumab was assumed to be █%, sourced from the MANDARA DB trial. This helped to inform the effect of a lower benralizumab discontinuation rate and OCS discontinuation in the first year of the model on the incremental cost-effectiveness analysis of benralizumab + SoC vs SoC.

- Scenario 13: combination of scenarios 6 & 11

The scenario 13 is combined scenarios 6 and 11. In this scenario, the discontinuation rate of benralizumab was assumed to be █%, sourced from the MANDARA OLE and a patient who discontinue OCS in the benralizumab arm do not discontinue benralizumab. Similar to scenario 12, this helped to inform the effect of OCS discontinuation in the first year of the model on the incremental cost-effectiveness analysis of benralizumab + SoC vs SoC but with a higher benralizumab discontinuation rate.

6.1.2.4 Utility

- Scenario 14: only refractory utility increased

The EAG base case is adjusted so that only the utility for refractory is increased by █. In the EAG base case, the utility is increased for both refractory and relapse states.

6.1.3 EAG subgroup analyses

No subgroup analyses conducted by the EAG.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 The EAG base case results

The EAG base-case was presented in Section 6.2. and Table 6.5 reports the individual impact of the changes proposed by the EAG to generate the EAG base-case results. The Appendix provides a short explanation of the changes were implemented in the CEM.

Table 6.5: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total LYs	Total QALYs	Increme ntal costs	Total LYs	Increme ntal QALYs	ICER (£/QAL Y)
CS base-case - Deterministic							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£26,092
SoC (OCS + IS)	██████	██████	██████	-		-	
CS base-case - Probabilistic							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£27,166
SoC (OCS + IS)	██████	██████	██████				
Matter of Judgement 1: Utility Estimates Adjustment							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£30,520
SoC (OCS + IS)	██████	██████	██████				
Matter of Judgement 2: Linear Reduction in OCS Discontinuation to 0 from Year 1 to Year 5							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£26,317
SoC (OCS + IS)	██████	██████	██████				
EAG base-case – Deterministic							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£30,798
SoC (OCS + IS)	██████	██████	██████				
EAG base-case - Probabilistic							
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£32,174
SoC (OCS + IS)	██████	██████	██████				

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Total LYs	Incremental QALYs	ICER (£/QALY)
Source: EAG base-case Excel Model Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; OCS = Oral Corticosteroids; SoC = Standard of Care; IS = immunosuppressants							

The adjustments made in the utility estimates did affect the QALY, by increasing the total utility values in the treatment and comparator arm. In addition, the incremental QALY was reduced, and it had a significant impact which led to an increase in the ICER to £30,520. Incorporating a linear reduction in OCS discontinuation to 0 from year 1 to year 5 impacted the cost in the treatment arm and increased the total incremental cost. The QALY estimates had a small decrease, which led to a slight dip in the incremental QALYs. The impact of linear reduction on OCS discontinuation did not have a very significant impact on the ICER. The EAG base-case was modelled by combining the changes to include utility adjustment and to incorporate a linear reduction in OCS discontinuation from years 1 to 5. The incremental cost-effectiveness of benralizumab increased to £30,798/QALY from £26,092/QALY deterministically, in the EAG base case, making it not cost-effective at WTP threshold of £30,000.

Table 6.6: EAG Base-case Result for Net Health Benefits

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
Benralizumab + SoC	██████	██████	£30,798	Not reported	-0.034
SoC (OCS + IS)	██████	-	-		

Source: EAG base-case Excel Model
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit;

Table 6.7: EAG Base-case Result for Net Monetary Benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000	NMB at £30,000
Benralizumab + SoC	██████	██████	£30,798	██████	██████
SoC (OCS + IS)	██████	-	-		

Source: EAG base-case Excel Model
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCS = oral corticosteroids; SoC = standard of care; IS = immunosuppressants.

Table 6.6 and Table 6.7 show the result of analysis in the updated model as adding benralizumab as an add on to SoC versus SoC alone, with WTP threshold of £30,000, delivered NHB and NMB equal to -0.034 and ██████, respectively. The results indicate that benralizumab + standard of care was not cost-effective.

6.2.2 EAG Deterministic Sensitivity Analysis

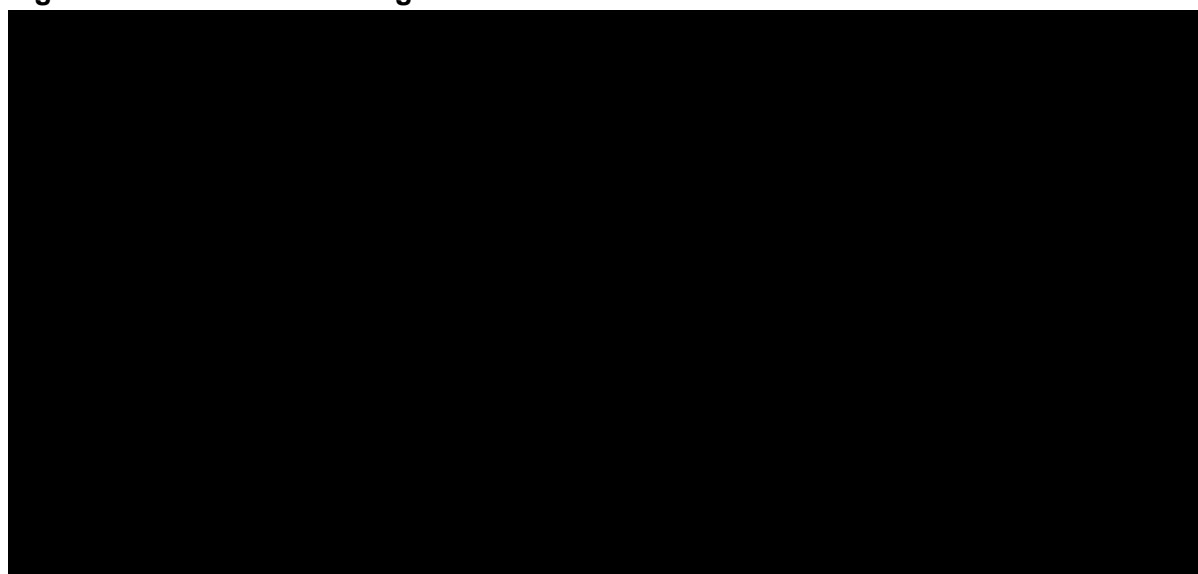
Table 6.8 and

Figure 6.5 present the results of deterministic sensitivity analysis of different parameters on the EAG base-case, highlighting the top 10 parameters with the greatest impact on the ICER. Health state utility (refractory) and the odds of achieving remission, derived from the Bucher ITC, remain as the variables with the greatest impact on cost-effectiveness results, which was also observed in the company base-case. All parameters were varied within their 95% confidence intervals, except mortality and unit cost parameters which were varied by $\pm 20\%$.

Table 6.8: EAG Deterministic Sensitivity Analysis

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Health state utilities: Refractory	██████	██████	██████
ITC: OR for odds of remission	██████	██████	██████
Health state utilities: Remission	██████	██████	██████
EGPA mortality: SMR for patients in remission	██████	██████	██████
Healthcare resource use: Remission	██████	██████	██████
Healthcare resource use: Stable disease	██████	██████	██████
OCS dosing: Daily dose of OCS for patients in stable disease	██████	██████	██████
Refractory disease: Risk reduction from baseline to week 52	██████	██████	██████
Life tables: Background mortality	██████	██████	██████
Disease management costs: Unit costs	██████	██████	██████
Source: EAG base-case Excel Model Abbreviations: ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; EAG = evidence assessment group; EGPA = eosinophilic granulomatosis with polyangiitis; SMR = standardised mortality ratio; OCS = oral corticosteroids.			

Figure 6.5: DSA tornado diagram for ICER for benralizumab versus SoC



Source: EAG base-case Excel model

Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OR = odds ratio; PAS = patient access scheme; QALYs = quality-adjusted life years; SMR = standardised mortality ratio; SoC = standard of care.

6.2.3 EAG Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis results for EAG base case are given in Table 6.9, Figure 6.6, Figure 6.7. The incremental cost-effectiveness of benralizumab + standard of care increased to £32,174/QALY, making it not cost-effective compared to the standard of care. Figure 6.6 is the cost-effectiveness plane that depicts the probabilistic sensitivity analysis for treatment and comparator. The cost-effectiveness of benralizumab + standard of care at different thresholds of willingness to pay is given in Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Figure 6.7.

Table 6.9: EAG base-case probabilistic sensitivity analysis result

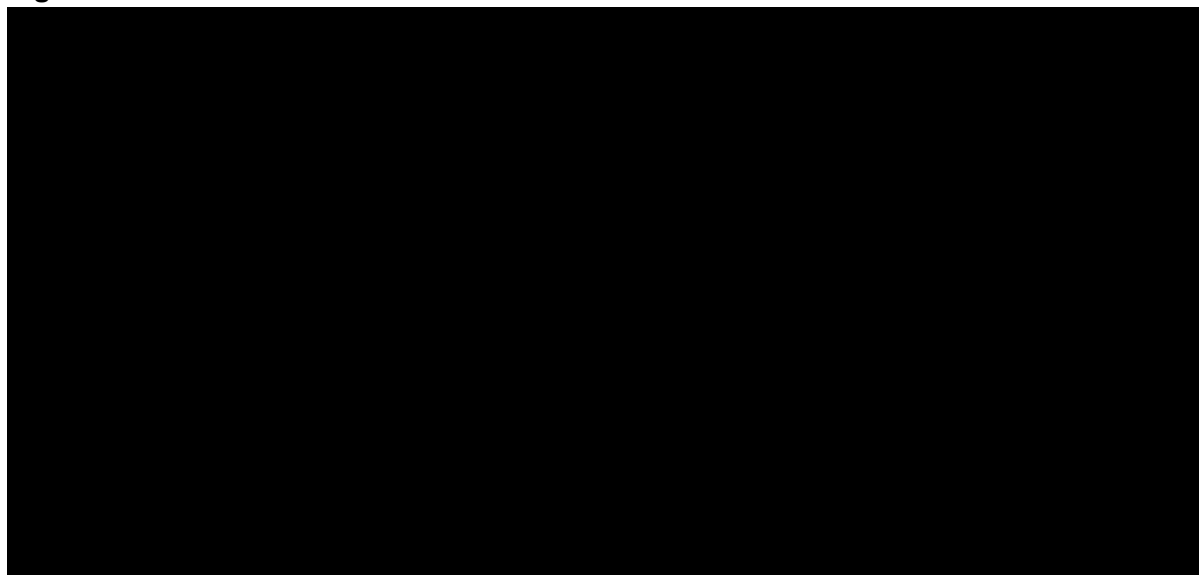
Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Benralizumab + SoC	██████	██████	██████	██████	██████	██████	£32,174
SoC (OCS + IS)	██████	██████	██████				

Source: EAG base-case Excel Model

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; OCS = oral corticosteroids; SoC = standard of care; IS = immunosuppressants.

The probability of benralizumab + standard of care was cost-effective against standard of care at a willingness to pay threshold of £30,000/QALY, in the EAG base case was ██████.

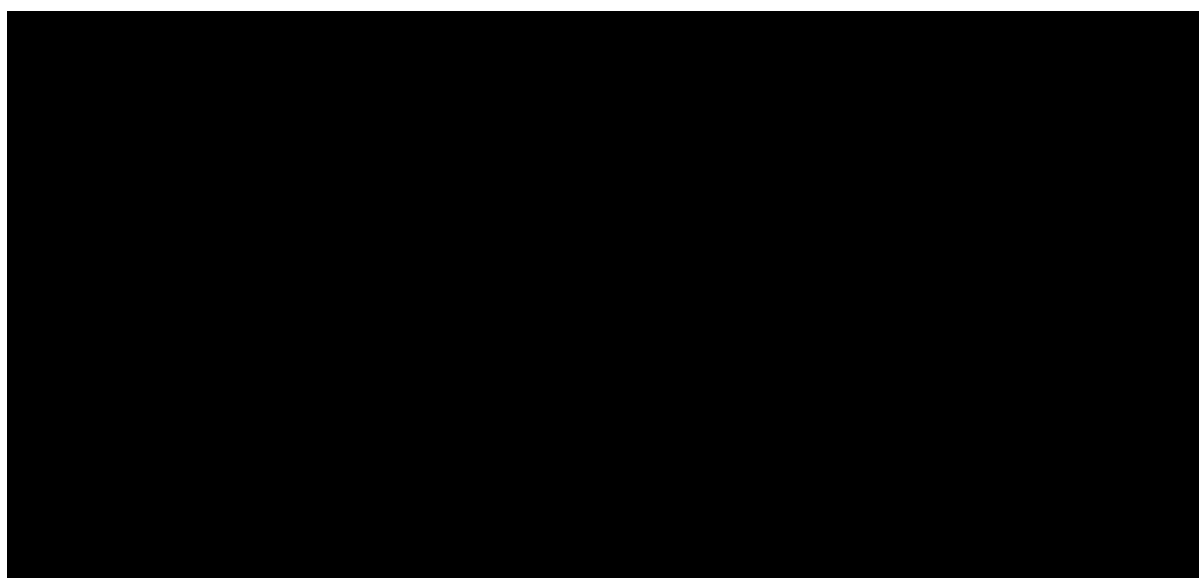
Figure 6.6: EAG base-case Cost-effectiveness Plane



Source: EAG base-case Excel Model

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year

Figure 6.7: EAG base-case Cost-effectiveness Acceptability Curve



Source: EAG base-case Excel Model

Abbreviations: EAG = evidence assessment group; SoC = standard of care

6.2.4 Company deterministic scenario analyses on the EAG base case

Table 6.10 shows the results from the company deterministic scenario analysis and their impact based on the EAG base case model. As is shown, benralizumab is not cost-effective in the base case and scenarios 1 and 2 and when the proportion of patients in refractory sub-state decreased by 5% in scenario 4.

The use of alternative health utility values in scenario 5 had significant impact on the incremental QALY which resulted in 60%-65% reduction in the ICER values (£16,093 and £13,700) and considered adding benralizumab as cost effective option at WTP threshold value of £30,000. However, since utility values provided for refractory state were extremely low, the EAG believes the source of utility valuation is not valid source.

Increasing the benralizumab discontinuation rate by 2% resulted in a reduction in the incremental cost (£16,093), QALYs (0.01) and ICER £29,416.

Increasing the proportion of patients in the refractory sub-state by 5% resulted a slight increase in incremental QALYs which resulted in the ICER value `

Table 6.10: Company deterministic scenario analyses on EAG base-case

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
	EAG base-case	N/A	N/A	£[REDACTED]	[REDACTED]	£30,798	-0.034
1	Relative efficacy of benralizumab versus SoC	informed by the Bucher ITC • OR for remission: [REDACTED] • RR for ARR: [REDACTED]	informed by MAIC • OR for remission: [REDACTED] • RR for ARR: [REDACTED]	£[REDACTED]	[REDACTED]	£30,290	-0.013
2	Health-state specific SMRs	informed by CPRD • Remission: [REDACTED] • Stable disease: [REDACTED] • Relapse: [REDACTED]	varied by +10%	£[REDACTED]	[REDACTED]	£31,229	-0.052
			varied by -10%	£[REDACTED]	[REDACTED]	£30,278	0.948
3	Annual discontinuation rate for benralizumab	• based on conservative midpoint of alternative sources by [REDACTED]%	midpoint of sources in Document B, ⁵ • [REDACTED]%	£[REDACTED]	[REDACTED]	£29,416	0.022
4	Proportion of patients in refractory sub-state, within stable disease health state	informed by MANDARA • Benralizumab arm: Starting % of [REDACTED] then relative reduction applied) to yield [REDACTED]% at week 52) informed by CPRD • SoC arm: starting	Reduction in Starting proportion by -5%	£[REDACTED]	[REDACTED]	£31,672	-0.070
			Increase in Starting proportion by +5%	£[REDACTED]	[REDACTED]	£29,990	0.000

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
		% of █████%, stayed constant					
5	Source of health state Utility	Adelphi DSP study ³	General population valuation from vignette study ³⁸	£████	████	£16,093	1.148
			Patient valuation from vignette study ³⁸	£████	████	£13,700	1.580
Source: EAG base-case Model Abbreviations: EAG = Evidence Assessment Group; ARR = annualised relapse rate; CPRD = Clinical Practice Research Datalink; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NHB = net health benefit; OR = odds ratio; PAS = patient access scheme; QALY= quality-adjusted life year; RR = risk ratio; SMR = standardised mortality ratio; SoC = standard of care; Adelphi DSP = Disease Specific Programmes							

6.2.5 EAG Exploratory Scenario Analysis

Table 6.11 shows the results of EAG exploratory scenario analysis on the EAG-base case. Scenario 6, 12 and 13 have the highest impact on ICER with values £33,338, £34,006, £33,157, respectively.

Table 6.11 EAG deterministic scenario analyses

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
	EAG base-case	N/A	N/A	██████	██████	£30,798	-0.034
1	Mortality	informed by CPRD • Remission: ██████ • Stable disease: ██████ • Relapse: ██████	Inclusion of OCS chronic event mortality hazard ratios A	██████	██████	£30,340	-0.016
2	Mortality	informed by CPRD • Remission: ██████ • Stable disease: ██████ • Relapse: ██████	Inclusion of OCS chronic event mortality hazard ratios B	██████	██████	£30,000	0.000
3	Soc with OCS effectiveness	RR of SoC with OCS vs SOC without OCS = 1	RR of SoC with OCS vs SOC without OCS = 2	██████	██████	£32,420	-0.099
4	Soc with OCS effectiveness	RR of SoC with OCS vs SOC without OCS = 1	RR of SoC with OCS vs SOC without OCS = 4	██████	██████	£33,012	-0.121

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
5	Soc with OCS effectiveness	RR of SoC with OCS vs SOC without OCS = 1	RR of SoC with OCS vs SOC without OCS = 8	██████	██████	£33,165	-0.126
6	OCS/benralizumab discontinuation assumption	Those who do discontinue OCS can discontinue benralizumab	All of those who discontinue OCS do not discontinue benralizumab	██████	██████	£33,388	-0.175
7	OCS/benralizumab discontinuation assumption	Those who have discontinued OCS while receiving benralizumab do not restart OCS after discontinuing benralizumab	Those who have discontinued OCS while receiving benralizumab restart OCS after discontinuing benralizumab	██████	██████	£33,165	-0.130
8	OCS discontinuation rate	OCS discontinuation rate declines linearly from 1 year to 5 years to 0%	OCS discontinuation rate drops to 0% after 12 months	██████	██████	£31,520	-0.065
9	OCS discontinuation rate	OCS discontinuation rate declines linearly from 1 year to 5 years to 0%	OCS discontinuation rate is constant for the duration of the model	██████	██████	£30,520	-0.022

#	Model aspect	Base-case	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£)	Incremental NHB (£30,000)
10	Benralizumab discontinuation rate	Benralizumab discontinuation rate of ■■■	Benralizumab discontinuation rate of ■■■	■■■	■■■	£33,372	-0.193
11	Benralizumab discontinuation rate	Benralizumab discontinuation rate of ■■■	Benralizumab discontinuation rate of ■■■	■■■	■■■	£28,743	0.045
12	Benralizumab discontinuation rate	Benralizumab discontinuation rate of ■■■	Combination of scenarios 6 & 10	■■■	■■■	£34,006	-0.237
13	Benralizumab discontinuation rate	Benralizumab discontinuation rate of ■■■	Combination of scenarios 6 & 11	■■■	■■■	£33,157	-0.152
14	Relapse utility	The utility for both refractory and relapse is increased from the CS model.	Utility for relapse the same as in the CS base case. Only the refractory utility is increased.	■■■	■■■	£30,203	-0.009

Source: EAG base-case Model

Abbreviations: EAG = Evidence Assessment Group; ARR = annualised relapse rate; CPRD = Clinical Practice Research Datalink; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NHB = net health benefit; OR = odds ratio; PAS = patient access scheme; QALY= quality-adjusted life year; RR = risk ratio; SMR = standardised mortality ratio; SoC = standard of care

6.3 Overall conclusions of the EAG's cost-effectiveness analysis

The estimated EAG base-case probabilistic ICER, based on the assumptions preferred the EAG highlighted in Section 5.1, was £32,174 per QALY gained, without using the PAS prices of treatments used in standard of care in EGPA patients. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of ■■■ and ■■■ at willingness to pay thresholds of £20,000 and £30,000 per QALY gained by patients on EGPA treatment. These results suggest that benralizumab + standard of care is not cost-effective in treating EGPA patients, when compared to the standard of care at those thresholds.

The adjustments made in the utility estimates for the refractory and relapse health states made a significant impact on the incremental QALY changing it from ■■■ in the company base-case deterministic analysis to ■■■ in the EAG base-case. The EAG had adopted a simple method of adding the average of disutilities associated with OCS complications to the utility values of refractory and relapse health states, to account for the potential double counting of the effect of disutilities associated with OCS related complications in the QALY estimates of the patients in the model. In total utility adjustment and assumption in OCS discontinuation increased the ICER from £26,092 in the deterministic company base-case to £30,798 in the EAG base-case deterministic analysis.

The simple method adopted in the EAG scenario to adjust for mortality associated with OCS complications had very little effect on the ICER. The benralizumab discontinuation rate scenarios changed the ICER by less than £3,000. The alternative OCS discontinuation rate assumptions explored increased the ICER by less than £1,000. This is due partly to ■■■ having discontinued OCS by 1 year, but mostly due to the model drivers being overwhelmingly the effect of benralizumab on the EGPA transition probabilities and the percentage of stable patients who are non-refractory.

Scenarios 6 and 12 affect the ICER the most by only a fraction because benralizumab discontinuation is also reduced in the scenario as well as increasing the percentage of patients who receive OCS while receiving SoC.

6.4 Overall conclusions of the EAG's critique

The company conducted SLRs focusing on the clinical effectiveness, cost effectiveness and HRQoL. The company conducted a SLR aimed at identifying evidence on the efficacy and safety of treatments for patients with EGPA, and a SLR to identify economic evaluations, HCRU, and HRQoL data in patients with EGPA, which informed the economic model. The methodology of the SLRs was overall considered to be appropriate by the EAG with some concerns regarding the search strategies and prioritisation decisions applied, leading to potentially relevant studies being missed.

To estimate the relative effectiveness of benralizumab compared to SoC in the absence of a head-to-head trial, the company evaluated the feasibility of conducting an anchored ITC. The company concluded that the only RCT that would enable an ITC with the pivotal trial MANDARA, was MIRRA. Both Phase III RCTs, the company reasoned that apparent differences in potential treatment effect modifiers between MIRRA and MANDARA were not clinically meaningful after consulting clinical experts. Subsequently the company generated a Bucher ITC, which demonstrated benralizumab treatment as an add-on treatment to OCS with or without IS, compared to SoC (OCS with or without IS), to provide substantial improvement in the proportion of patients with EGPA in remission and a reduced annualised relapse rate.

The company validated the latter two outcomes in a MAIC, which was adjusted using a pooled rank-ordered list of potential treatment effect modifiers. The EAG are satisfied with this approach to managing potential effect modifiers within the ITC.

The EAG is concerned that the CS did not meet the NICE scope with regards to the patient population and treatment comparator. Firstly, the MANDARA and MIRRA trial populations excluded patients with severe EGPA. Secondly, owing to the exclusion of patients with severe disease, the company selected OCS with or without IS as the comparator for benralizumab (in addition to OCS with or without IS). The EAG's clinical advisor confirmed agents such as cyclophosphamide and rituximab have limited use in patients with non-severe EGPA, but stated that benralizumab would likely be used for patients with severe disease in clinical practice. The EAG have therefore raised this as a key issue, highlighting to the NICE committee that the evidence provided here on the clinical effectiveness of benralizumab is based on patients with non-severe EGPA. Hence the evidence from the company's trial and ITC in this submission may not be generalisable across the whole patient population i.e. patients with severe EGPA.

Benralizumab affects costs and QALYs through the effect on the numbers of patients in the EGPA remission/stable/relapse states, and through the proportion of patients receiving OCS treatment. An increase in patients in remission increases quality of life and reduces treatment cost and it also reduces the average OCS use and thereby the incidence of OCS-associated acute events and prevalence of OCS-associated chronic events.

Benralizumab affects EGPA states in two ways: (1) making it more likely that patients will be in the remission state and less likely they will be in the stable and relapse states, and (2) making it more likely that patients will be in the non-refractory state than in the refractory state for the patients who are considered to be stable. These are the two big drivers of the model. The evidence for the effect of benralizumab on patients achieving response (remission) and for reducing relapses came from an ITC. The EAG did not identify any significant risk of bias in the ITC estimate due to the differences in the effect modifiers between the trials included in the ITC. The evidence for the reduction of patients in the refractory state came from the MANDARA trial. The company assumed that benralizumab would have the same effectiveness for the duration of treatment (no treatment waning). This was justified with reference to a previous appraisal, and clinical experts suggested this was plausible.

Benralizumab reduced the proportion of patients receiving OCS in the model. Responders to treatment and non-responders were equally likely to discontinue OCS treatment. Patients who had discontinued treatment did not restart OCS treatment if they discontinued benralizumab. Patients were equally likely to be in remission if they received SoC with OCS or if they received SoC without OCS. The EAG could not find supporting evidence or justification for these implicit assumptions in the CS, and consequently explored removing these assumptions in EAG analyses. The alternative assumptions explored increase the ICER by less than £3,500, although assuming that those who discontinued OCS never discontinued benralizumab increased the ICER by £7,723.

The source of utility estimates for the EGPA states appeared to include patients with organ damage that could be attributed to OCS-associated acute and chronic events. Since disutilities of OCS-associated acute and chronic events were included separately in the model, this may mean that the utility estimate for worse EGPA states associated with higher average OCS dose may be underestimated relative to other EGPA states. The EAG addressed this in the

EAG base case, although there is considerable uncertainty in any utility adjustment given a lack of evidence.

There was significant uncertainty in benralizumab and OCS discontinuation rates, and this was explored in scenario analyses.

The company base-case suggested that, after applying the PAS discount to the unit cost of benralizumab, benralizumab had an ICER of £26,092, increasing QALYs by [REDACTED] and increasing costs by [REDACTED] in the probabilistic analysis, with a [REDACTED] probability of being cost-effective at a £20,000 threshold and a [REDACTED] probability of being cost-effective at a £30,000 threshold.

The EAG found no errors in the CEM after an initial revision by the company. The EAG base-case increased the utility estimates for the refractory and relapse states, and decreased the OCS discontinuation rate after 1 year. The EAG base-case suggested that, after applying the PAS discount to the unit cost of benralizumab, benralizumab had an ICER of £30,798, increasing QALYs by [REDACTED] and increasing cost by [REDACTED], with a [REDACTED] probability of being cost-effective at a £20,000 threshold and a [REDACTED] probability of being cost-effective at a £30,000 threshold.

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8 Appendices

8.1 A.1 Survival model

Incorporation of OCS chronic event mortality rates was explored using a simple way of including it in the model.

In the CS model, the mortality effect of EGPA was incorporated by including mortality hazard ratios for remission (1.5), stable (2.27) and relapse (3.33) states versus the general population mortality. The EAG was interested to explore the impact of incorporating OCS chronic event mortality hazard ratios in the model. As the risk of OCS chronic events increases over time, the expectation is that hazard ratios versus the general population may increase over time.

The risk of OCS acute and chronic events in the CS model was modelled based on the evidence from Gibson et al (2024).⁷ The same publication reported HRs for the chronic events versus the absence of the chronic events. The Gibson et al. (2024)⁷ mortality HRs are presented in Table 6.1. There are two common ways of implementing HRs: (1) multiplying HRs together, and (2) assuming that event HRs are the same or similar regardless of whether or not a person has EGPA.

Table A.1: Morality hazard ratios vs EGPA/no event

Event	Gibson et al, 2024 ⁷
	vs no event
T2DM	2.07
eCVD	1.28
OP	1.36
T2DM/eCVD	2.07
T2DM/OP	8.50
eCVD/OP	1.36
T2DM/eCVD/OP	8.50
Source: EAG base-case Excel Model	
Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroid; OP = Osteoporosis; EGPA = eosinophilic granulomatosis with polyangiitis; T2DM = type 2 diabetes mellitus	

Table A.2: Hazard ratios versus the general population

Health State	Event	EAG Survival A (Scenario 1)	EAG Survival B (Scenario 2)
		vs gen pop	vs gen pop
Remission	Event free	1.01	1.01
	T2DM	3.11	2.16
	eCVD	1.92	1.70
	OP	2.04	1.75
	T2DM/eCVD	3.11	2.16
	T2DM/OP	12.75	4.37
	eCVD/OP	2.04	1.75
	T2DM/eCVD/OP	12.75	4.37
Stable	Event free	1.52	1.52
	T2DM	4.70	3.27
	eCVD	2.91	2.57
	OP	3.09	2.65
	T2DM/eCVD	4.70	3.27
	T2DM/OP	19.30	6.62
	eCVD/OP	3.09	2.65
	T2DM/eCVD/OP	19.30	6.62
Relapse	Event free	2.23	2.23
	T2DM	6.89	4.79
	eCVD	4.27	3.77
	OP	4.53	3.88
	T2DM/eCVD	6.89	4.79
	T2DM/OP	28.31	9.71
	eCVD/OP	4.53	3.88

	T2DM/eCVD/OP	28.31	9.71
Source: EAG base-case Excel Model			
Abbreviations: eCVD = established cardiovascular disease; OCS = oral corticosteroid; OP = Osteoporosis; EGPA = eosinophilic granulomatosis with polyangiitis; T2DM = type 2 diabetes mellitus			

Event hazard ratio calibration

Hazard ratios for each of the events in Table A.2 were created compared to no event and these were then multiplied by the remission/stable/relapse hazard ratios to derive the hazard ratios that are presented in Table A.2.

For no event, the HR was 0.67, which was the smallest it could be so that in the remission state the no event HR versus the general population was >1. Of course, the HR could be anywhere between 0.67 and 1.

HRs for the events were calibrated according to the same factor as an exponential. T2DM was the primary event HR to calibrate. The HR for T2DM in the remission state was 2.16 versus the general population in Table A.2. This is close to the Gibson et al, HR of 2.07 shown in Table A.1.

Changes in the model trace

The OCS chronic event trace in columns CX to DD in the Benralizumab sheet was edited so that each chronic event had a weighted average of the mortality risk according to the number of patients in each state (remission/stable/relapse). For example, for T2DM

$$= ((\$D E16 * \$A J16) + (\$D F16 * (1 - \$A M16 - \$A N16))) * (1 - (\text{HR\_REM\_T2DM} * \$C E16 * \$Z16 + \text{HR\_STB\_T2DM} * \$C F16 * \$A A16 + \text{HR\_RLP\_T2DM} * \$C G16 * \$A B16) / \text{SUM}(\$C E16 : \$C G16))$$

Where HR_REM_T2DM*\$Z16 is the hazard ratio for remission for T2DM versus the general population.

The weighted average of the OCS chronic event mortality hazard ratios was calculated:

$$= (\text{DE16} * (\text{HR\_REM\_Event\_free} * \text{EC16} + \text{HR\_STB\_Event\_free} * \text{EA16} + \text{HR\_RLP\_Event\_free} * \text{EF16}) / \text{SUM}(\text{EC16}, \text{EA16}, \text{EF16})$$

$$+ \text{DF16} * (\text{HR\_REM\_T2DM} * \text{EC16} + \text{HR\_STB\_T2DM} * \text{EA16} + \text{HR\_RLP\_T2DM} * \text{EF16}) / \text{SUM}(\text{EC16}, \text{EA16}, \text{EF16})$$

$$+ \text{DG16} * (\text{HR\_REM\_eCVD} * \text{EC16} + \text{HR\_STB\_eCVD} * \text{EA16} + \text{HR\_RLP\_eCVD} * \text{EF16}) / \text{SUM}(\text{EC16}, \text{EA16}, \text{EF16})$$

$$+ \text{DH16} * (\text{HR\_REM\_OP} * \text{EC16} + \text{HR\_STB\_OP} * \text{EA16} + \text{HR\_RLP\_OP} * \text{EF16}) / \text{SUM}(\text{EC16}, \text{EA16}, \text{EF16})$$

+DI16*(HR_REM_T2DM_eCVD*EC16+HR_STB_T2DM_eCVD*EA16+HR_RLP_T2DM_eCVD*EF16)/SUM(EC16,EA16,EF16)

+DJ16*(HR_REM_T2DM_OP*EC16+HR_STB_T2DM_OP*EA16+HR_RLP_T2DM_OP*EF16)/SUM(EC16,EA16,EF16)

+DK16*(HR_REM_eCVD_OP*EC16+HR_STB_eCVD_OP*EA16+HR_RLP_eCVD_OP*EF16)/SUM(EC16,EA16,EF16)

+DL16*(HR_REM_T2DM_eCVD_OP*EC16+HR_STB_T2DM_eCVD_OP*EA16+HR_RLP_T2DM_eCVD_OP*EF16)/SUM(EC16,EA16,EF16))/SUM(DE16:DL16)

This references columns DF:DL instead of CX:DD in the CS model.

This weighted average increases over time as the number of patients with specific chronic events increases. Patients with chronic events die at a greater rate so some numbers eventually decrease.

The mortality risks in column BC in the original CS model are then edited:

=IF((baseDemAgeUsed+\$E16)<101,((SUM(\$BK16,\$BN16,\$BQ16,\$BT16,\$BW16,\$BZ16)*Z16*DN16)+(SUM(\$BL16,\$BO16,\$BR16,\$BU16,\$BX16,\$CA16)*AA16*DN16)+(SUM(\$BM16,\$BP16,\$BS16,\$BV16,\$BY16,\$CB16)*AB16*DN16))/SUM(\$BK16:\$CB16),1)

Where DN is the weighted hazard ratio for the OCS chronic events.

Finally, the columns BG:BY in the original CS model are edited so that the state-specific mortality risks are multiplied by the weighted average of the OCS chronic event hazard ratios.

8.2 A.2 Scenario 6

This model assumes that those who discontinue OCS do not discontinue benralizumab.

First, 3 columns were created in the EGPA trace for those who discontinue OCS. In the CS model, these patients are lumped with those who never started OCS.

Second, those who discontinue OCS never move to SoC.

Third, after 1 year 75% of those who had not discontinued OCS were assumed to be responders and move to SoC. This equates to about 65% response, and approach similar to the original CS model rather than the post-clarification model.

Fourth, the response rate, benralizumab discontinuation rate during the first 12 months, the benralizumab discontinuation rate after 12 months, and the OCS discontinuation rate during the first 12 months were calibrated to so that

- The number who had discontinued benralizumab by cycle 14 the cumulative number of people who had discontinued benralizumab was 50, and the cumulative number of people who had discontinued OCS was 345.
- The number who had discontinued benralizumab by cycle 130 the cumulative number of people who had discontinued benralizumab was 151.

8.3 A.3 Scenario 7

This scenario assumes that all those who discontinue OCS, restart OCS when they discontinue benralizumab. So these patients transition to the SoC with OCS states.

First, 3 columns were created in the EGPA trace for those who discontinue OCS. In the CS model, these patients are lumped with those who never started OCS.

Second, those who discontinue OCS are transitioned to SoC with OCS.

Third, after 1 year response transitions were treated as in the post-clarification CS model.

The benralizumab discontinuation rate during the first 12 months, the benralizumab discontinuation rate after 12 months, and the OCS discontinuation rate during the first 12 months were calibrated to so that

- The number who had discontinued benralizumab by cycle 14 the cumulative number of people who had discontinued benralizumab was 50, and the cumulative number of people who had discontinued OCS was 345.
- The number who had discontinued benralizumab by cycle 130 the cumulative number of people who had discontinued benralizumab was 131.

8.4 A.4 SoC with OCS versus SoC without OCS efficacy

This model explores different relative risks for SoC with OCS versus SoC without OCS.

Starting from the post-clarification model.

First, the proportion of patients receiving SoC who receive OCS was calculated for each cycle in the EGPA trace.

Second, the RR of SoC with X% of patients receiving OCS versus SoC with 86% of patients receiving OCS for each cycle using the following formula:

$$RR = \frac{1 - \alpha + \alpha * RR_{OCS-noOCS}}{0.14 + 0.86 * RR_{OCS-noOCS}}$$

Where α is the proportion of patients receiving SoC who receive OCS for each cycle in the EGPA trace.

Third, the SoC transition probabilities with and without OCS were multiplied or divided by RR, so that if RR was <1 then it was less likely that a patient would transition to the remission state and it would be more likely to transition to the relapse state.

Fourth, $RR_{OCS-noOCS}$ was varied between 2, 4 and 8 in the scenario analyses.

Single Technology Appraisal

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 24 February 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Please note the approach adopted by the Company throughout is as follows:

- Proposed additions in **bold**
- Proposed amendments in **abe** and proposed suggestions in **abc**

Section 1: Factual inaccuracies on EAG’s key issues

Issue 1: “Company’s trial and ITC results may not be generalisable to all EGPA patients (i.e. those with severe EGPA)”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.3, Table 1.2 Page 32, Section 2.1 Multiple other locations throughout the EAG report	The Company would request clarifying, throughout the EAG report, that the CS covers the clinical and cost effectiveness of benralizumab in patients with non-severe EGPA (defined as not organ- or life-threatening), in line with the available evidence. The Company also requests consistency in defining “severe” patients throughout the EAG report – please see below.	The Company would like to clarify that the intended positioning of benralizumab is in patients with non-severe EGPA (defined as not organ- or life-threatening). See Error! Not a valid bookmark self-reference. (Figure 5 in CS) presents the proposed positioning for benralizumab is as an add-on treatment for adult patients with relapsing or refractory EGPA who are receiving OCS with or without stable IS therapy, as validated by clinical experts.	The EAG have now clearly defined severe vs non-severe disease in Section 2.1 (e.g. patients with organ or life-threatening EGPA (hereafter referred to as severe EGPA)). This change has been implemented throughout the document. When the EAG discuss severity levels, we explicitly state this refers to the non-severe population. We have added the CS Figure 1 (detailed below) in Section 2.1 for clarity and

		Figure 1 in Appendix, which illustrates the proposed positioning of benralizumab. This population is aligned with MANDARA, where patients with severe EGPA (defined as organ- or life-threatening) were excluded from the trial, for reasons provided in the CS and response to the EAG's clarification letter. It is understandable that clinicians express an interest in using benralizumab in this setting, given limited treatment options; however, the intended positioning of benralizumab is not in patients <i>currently experiencing severe</i> EGPA (defined as organ- or life-threatening). Notably, there is evidence supporting the use of benralizumab in patients with a <i>history of severe</i>	have also in this section highlighted the post-hoc results presented in Hellmich et al. (2024).{Hellmich, 2024 #118}

		<i>disease</i> (defined as organ- or life-threatening), making these patients eligible for treatment, since they could have been included in the MANDARA trial. Evidence presented at ACR 2024 highlights a post hoc analysis of the MANDARA trial results, stratified by the severity of patients' EGPA-associated cumulative manifestations. This analysis considered patients with a history of severe disease (experienced severe disease >3 months before MANDARA enrolment) according to specific criteria outlined in their medical history.	
Page 14, Section 1.3, Table 1.2	Please consider amending the text as follows: “However, both studies excluded patients presenting with organ- or life-threatening EGPA at the time of screening.”	Patients who previously had organ- or life threatening EGPA could theoretically be included	The EAG agrees with the company's proposed amendment. Text amended.

Multiple locations throughout the EAG report When referring to “severe patients” throughout	Consistency is requested in defining “severe” patients throughout the EAG report. Severe patients should consistently be defined as those with “organ- or life- threatening disease”. This population should be clearly distinguished from the “non-severe patients” (those without organ- or life-threatening disease). The Company acknowledges that a spectrum of severity exists <i>within</i> the non-severe population, and requests that this is clarified in all instances throughout the report.	Based on the available evidence package and the proposed positioning of benralizumab, it is essential to differentiate between patients with severe (organ- or life-threatening disease) and non-severe (not organ- or life-threatening disease) patients, and to maintain consistency in these definitions throughout the report	The EAG agrees with the company’s proposed amendment. Definitions for severe and non-severe disease have been stated in section 2.1 and terms have been applied throughout.

Issue 2: “EGPA state utility estimates”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 122, Section 6.1.1.1	Please amend the wording to state: “The EAG made the assumption that those in the stable refractory and relapse states are more likely to have organ damage than those in the non-refractory and remission states, the EAG increased the utility in the refractory and relapse states by *****,	Minor wording correction	The EAG agrees and made the change in the text.

	the average disutility across all of the acute and chronic events.”		
Page 93, Section 4.2.6	Please consider removing this statement. “* out of 177 participants were children below the age of 18 years, who participated completing the EQ-5D-5L questionnaire, which may not be a suitable instrument for measuring quality of life in children and young adults.”	The Company can confirm that the minimum age of patients included in the Adelphi DSP who had an EQ-5D-5L score (n=177) was ** years. EQ-5D-5L is appropriate for use in people aged 12 years and older	The EAG agrees with the suggested recommendation. This point has been removed from the text.
Page 132, Section 6.1.2.4	Please amend the wording to state: “The EAG ~~base-case~~ ~~scenario analysis~~ is adjusted so that only the utility for refractory is increased by *****. In the EAG base case, the utility is increased for both refractory and relapse states.”	Minor wording correction	This sentence means that the EAG base-case which had refractory and relapse states utilities adjusted was changed so that only the refractory state utility was increased by *****. The changes proposed by the company do not convey this meaning.

Issue 3: “Discontinuation rate of benralizumab”

No factual inaccuracies identified.

Issue 4: “The relationship between benralizumab discontinuation and OCS discontinuation”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Section 1.3	Please consider amending the text as follows: “Additional observational data on the use of benralizumab over time would help inform benralizumab discontinuation rates in EGPA.”	Clarification is requested as this evidence is available from asthma – but not specific to EGPA	The EAG edited the text to reflect the proposed change. The EAG have considered the benralizumab discontinuation rates sourced from MANDARA DB and MANDARA OLE trials in the EAG scenarios. The benralizumab discontinuation rates observed in severe eosinophilic asthma patients were mentioned here because it was part of the discussion in CS submission. This was used to indicate as a source of additional evidence on uncertainty of benralizumab discontinuation rates, apart from the evidence from MANDARA trials.
Page 17, Section 1.3	Please consider amending the text as follows:	Minor wording correction	The EAG agrees with the company’s proposed

	“Removing any one of the assumptions results in increased costs and lower QALYs for benralizumab and therefore a ~~lower~~ higher ICER.”		amendment and the text was changed accordingly.

Issue 5: “OCS discontinuation rate: the OCS discontinuation rate was assumed to be constant at 38% per year. This may be unrealistic”

No factual inaccuracies identified.

Issue 6: “No treatment waning”

No factual inaccuracies identified.

Section 2: Other factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Section 1.2	Please consider amending the text as follows: “Response rate: Increase the proportion of patients who achieve remission. This affects QALYs in ~~two~~ three ways: (1) through the higher utility associated with the remission state, (2) the lower OCS dose, which results in lower disutility associated with OCS-associated acute and chronic adverse events, (3) and	In the model, patients in remission have a lower SMR than those in stable disease or relapse health states. Benralizumab treatment increases the proportion of patients who achieve remission, leading to lower mortality and extended survival, which increases the QALYs for this patient population.	The EAG agrees that this is a reasonable amendment, and this has been made.

	through a lower SMR than the stable disease or relapse health states.	Therefore, for completeness, the Company suggests mentioning the modelled impact of benralizumab treatment on survival as this also increases QALYs	
Page 32, Section 2.1	Please consider amending the text as follows: “Clinical advice to the EAG indicated that benralizumab would also benefit the population with severe disease (defined as organ- or life-threatening) who are more likely than the wider EGPA population to be receiving treatment with cyclophosphamide and, to a lesser extent, rituximab.”	Context should be added to emphasise that the perceived clinical benefit from experts was not confined to this population	The text has now been amended and restructured to reflect this.
Page 32, Section 2.1 Page 33, Section 2.1	The paragraphs on pages 32 and 33 are contradictory, so please amend to be consistent: "Based on clinical advice to the EAG, it is possible that relapses (either during the trial or after follow up) might be severe enough to instigate organ or life-threatening disease manifestations, and therefore there is a possibility that	Page 32 states that the “ineligible patients” would increase and page 33 states that the “eligible patients” would increase. Please refer to Company’s response to Issue 1 and Figure 1 in Appendix for	The first statement has now been amended: Based on clinical advice to the EAG, it is possible that relapses (either during the trial or after follow up) might be severe enough to instigate organ or life threatening disease

	the portion of patients who would be ineligible for benralizumab using the MIRRA/MANDARA criteria would increase over time" "If the MANDARA trial inclusion criteria were adopted in real-world clinical practice, the proportion of EGPA patients eligible for benralizumab will likely increase as patients previously severe become eligible as their disease stabilises, and patients whose disease has relapsed with organ-or life-threatening manifestations may not meet the proposed stopping criteria to withdraw treatment. "	intended positioning of benralizumab	manifestations, and therefore there is a possibility that the proportion of patients who would be eligible for benralizumab using the MIRRA/MANDARA criteria would increase over time.
Page 55, Section 3.2.1.1	Please amend the text to reflect that the Company did not confirm this – rather, it was discussed during the clarification call that the Company would try to determine the likelihood of this occurrence. Furthermore, the Company requests the EAG to provide commentary on whether this would impact the results in a significant manner. ***** *****	Please note that while theoretically possible, the Company assesses the likelihood of this occurrence as highly unlikely. Since MIRRA was conducted 5 years prior to MANDARA, many patients transitioned into the Long-term Access Programme (LAP), rendering them ineligible for MANDARA	The text has now been amended (including referencing the text the Company provided in the FAC document). {AstraZeneca plc, 2025 #117}

	over time as this is based on cumulative dose.		there is no mechanism in the model by which the effect of the intervention on OCS complications results in changes in mortality.”
Page 81, Section 4.2.1 Page 92, Section 4.2.5 Page 93, Section 4.2.6	Please ensure that the text describing the impact of excluding IS-related AEs from the modelling is consistent throughout the report – see below for inconsistencies: “The adverse events associated with IS treatment were not included in the CS model. IS treatment has a different mechanism of action to OCS, and the adverse events are different. This could have an impact on the cost and quality of life of the patients. So, the EAG has some concerns about excluding the IS adverse events.” “But the company adopted a conservative approach of not including the disutilities and cost associated with IS adverse events in the cost-effectiveness analysis. The EAG has concerns about not including the IS adverse events in the CS model	Updates to wording requested to be consistent throughout report	Thank you. The EAG has edited each incidence with: “IS adverse events were excluded from the model. These are likely different to adverse events associated with OCS due to a different mechanism of action. This is likely conservative with respect to benralizumab since a patient is less likely to receive IS and therefore experience fewer IS adverse events.”

	because it might have an impact on the cost-effectiveness analysis.” “The adverse events of IS treatment were not included in the model. This might have a potentially significant impact on the EGPA patients HRQoL.”		
Page 82, Section 4.2.2.1	Please consider amending the text as follows: “Following a query in the clarification letter (Question B11), ~~on responders for benralizumab after 1 year at 12 months which include all patients, the company update the model and only patients in the remission state transitioned to the responder subgroup.~~” regarding benralizumab response at 52 weeks, the Company updated the model so that all patients who respond to treatment at 52 weeks (defined as remission; BVAS=0 and an OCS dose ≤4 mg/day) continue to receive benralizumab, while all patients in the stable or relapse states (and therefore not in remission) do not respond and therefore discontinue benralizumab treatment, going on to receive SoC.”	Minor updates to the wording to explain the model correction	The EAG agrees with the company’s proposed amendment. Text amended.

Page 85, Section 4.2.2.4	Please consider amending the text as follows: “It was assumed by the company that all patients who respond to the treatment will continue to receive benralizumab for the rest of their lifetime except for those who discontinue based on general attrition rates”	Patients who respond to treatment with benralizumab are still at risk of discontinuing treatment based on general rates of attrition	The EAG agrees with the company’s proposed amendment. Text amended.
Page 100, Section 4.2.7.1	Please consider amending the text below to reflect that Figure 7 is not indicative of the rate of OCS discontinuation: “The change in average dose over time in Figure 7 suggests that the same rate of OCS discontinuation may not persist for ever.”	Figure 7 presents the mean <i>dose</i> of OCS, not the <i>rate</i>	The EAG has edited the text as follows: “While Figure 7 presents the change in average dose over time, rather than the rate of OCS discontinuation, if it is possible to infer change in rate of OCS discontinuation from average dose then it may suggest that <u>the same rate of OCS discontinuation may not persist for ever.</u>”
Page 136, Section 6.2.2 Table 6.8	Please consider adding detail around approach adopted for “lower bound/upper bound”	E.g. these were based on +/-20%	EAG added this sentence for all of the tables on deterministic sensitivity analysis.

			“All parameters were varied within their 95% confidence intervals, except mortality and unit cost parameters which were varied by $\pm 20\%$.”

Section 3: Typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18, Section 1.3	Please correct the following typo: “The effect on the ICER of removing assumption (3) is very small unless OCS has a considerable effect on the likelihood of ~~in~~ being in better EGPA states.	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 20, Section 1.4, Table 1.7	Please amend the caption of Table 1.7 to state: “Probabilistic results from company ~~and EAG~~ base-case”	Typographical error	Table 1.7 shows results of probability sensitivity analysis of company base-case and EAG base-case, which was exactly meaning of the caption. So, the EAG reject the correction proposed by the company. The caption was amended

			to bring further clarity to the meaning.
Page 79, Section 4.2.1	Please correct the following typo: “CPRD ⁸ was used by the company as a representative source of UK clinical practice to ~~drive~~ ~~derive~~ baseline characteristics of patients entering the model as well as the proportion of patients in chronic comorbidities defined in the OCS sub-model.”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 73, Section 4.1	Please correct the following typo: In two of the searches a ‘combination ~~line~~ ’ did not include all relevant lines resulting in ‘orphan lines’.	Typographical error	The EAG have made this amendment.
Page 91, Section 4.2.4.1	Please amend the wording to state: “the odds ratio of ~~response~~ ~~remission~~ at 12 months”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 91, Section 4.2.4.1	Please amend the wording to state: “the annualised relapse rate ratio (ARR) ~~and 12 months.~~ ”	Typographical error	The EAG have updated the text to read, “the annualised relapse rate ratio (ARR) at 12 months.”
Page 127, Section 6.1.2.2	Please amend the wording to state:	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.

	“The greater the rate of benralizumab discontinuation , the lower the ICER for benralizumab”		
Page 92, Section 4.2.5	Please amend the wording to state: “The common chronic comorbidities ~~associate~~ associated with OCS treatment were T2DM, Cardiovascular disease (eCVD) and Osteoporosis.”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 94, Section 4.2.6.1	Please amend the wording to state: “They were generated using ~~SF-6~~ SF-36 and then mapped to EQ-5D-3L which was recommended by the NICE reference case”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 95, Section 4.2.6.1 Page 122, Section 6.1.1.1	Please amend the wording to state: “[...] everyone in refractory and relapse states in the Adelphi ~~DPS~~ DSP study has one and only one acute or chronic OCS event in equal numbers”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 102, Section 4.2.7.4	Please amend the wording to state: “These AEs can have an impact on the adverse events costs incurred ~~to~~ by the patient.”	Typographical error	The EAG agrees with the company’s proposed amendment. Text amended.

Page 125, Section 6.1.2.1 Figure 21	Please amend the figure legend to state: “ ~~ESG~~ EAG benralizumab”	Typographical error	The EAG has added a clarification footnote to the figure: “ <u>EAG Benralizumab</u> should read <u>EAG Benralizumab</u> ”
Page 61, Section 3.2.2.1	Please amend to the following: “The MANDARA trial was conducted in ~~54~~ 50 centres across nine countries”	Data error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 67, Section 3.3.1.3	Please amend to the following: “The difference in the timing of the two trials is also relevant; MIRRA took place prior to the coronavirus disease 2019 (COVID-19) pandemic (February 2014– ~~June 2015~~ September 2016), while MANDARA took place before/during the pandemic (October 2019–August 2023).”	Data error	The EAG have made this amendment and referenced the clinicaltrials.gov reference.{NCT02020889, 2013 #45}
Page 67, Section 3.3.1.3	Please amend the values as follows: “In the latter trial, COVID-19 was the most common adverse event, experienced by 21% (15/70) and ~~19% (27/70)~~ 27% (19/70) of patients in the benralizumab and mepolizumab groups respectively”	Data error	The EAG agrees with the company’s proposed amendment. Text amended.

Page 71, Section 3.4	Please amend the values as follows: “The study met its primary endpoint with benralizumab treatment resulting in remission (BVAS = 0 and OCS dose ≤4 mg/day) of EGPA in ~~58%~~ 57.7% patients, which was non inferior to mepolizumab treatment (~~56%~~ 56.5%).”	Data error	The EAG have made this amendment. However, we note that the Wechsler et al. (2024){Wechsler, 2024 #30} trial paper has rounded the percentages to whole numbers so instead we have cited Document B. {AstraZeneca plc, 2024 #13}
Page 91, Section 4.2.3.5, Table 4.4, row 3	Please amend “***** to *****”	Data error	The value provided in the clarification letter is 2.34, so the EAD did not make this amendment.
Page 142, Section 6.2.5, Table 6.11	Please amend the incremental QALYs for scenario 2 from ***** to *****	Data error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 142, Section 6.2.5, Table 6.11	Please amend the incremental NHB for scenario 2 from ***** to *****	Data error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 144, Section 6.2.5, Table 6.11	Please amend the incremental costs for scenario 14 from £***** to £*****	Data error	The EAG agrees with the company’s proposed amendment. Text amended.
Page 144, Section 6.2.5, Table 6.11	Please amend the incremental QALYs for scenario 14 from ***** to *****	Data error	The EAG agrees with the company’s proposed amendment. Text amended.

Page 144, Section 6.2.5, Table 6.11	Please amend the ICER for scenario 14 from £29,320 to £30,203	Data error	The EAG agrees with the company's proposed amendment. Text amended.
Page 144, Section 6.2.5, Table 6.11	Please amend the incremental NHB for scenario 14 from 0.003 to -0.009	Data error	The EAG agrees with the company's proposed amendment. Text amended.
Page 90, Section 4.2.3.4 Table 4.6	The proportions of patients with co-morbidities are incorrect. Please see Table 2 below for the updated proportions which align with the model shared with the Company.	Data error	Thank you for reporting this. The table numbers in the EAG report have been edited using the values reported in Table 3 in the appendix.

Section 4: Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.3, Table 1.3, row 1, page 14	“*** of the 177 participants suffered from various organ damage, which are severe adverse events, due to EGPA and the treatment received”	Please amend the confidentiality highlighting as follows: “*** of the 177 participants suffered from various organ damage, which are severe adverse events, due to EGPA and the treatment received”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 15 and 16, Section 1.3	“The company assumed a discontinuation rate of % per year for benralizumab in the CS model.”	Please amend the confidentiality highlighting as follows: “The company assumed a discontinuation rate of % per year for benralizumab in the CS model.”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 16, Section 1.3	“the discontinuation rate observed in the MANDARA DB trial was %.”	Please amend the confidentiality highlighting as follows: “the discontinuation rate observed in the MANDARA DB trial was %.”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 16, Section 1.3	“the discontinuation rate informed by MANDARA OLE was %.”	Please amend the confidentiality highlighting as follows:	The EAG accepted the proposed changes from the company and the format in the report was changed.

		“the discontinuation rate informed by MANDARA OLE was *%.”	
Page 16, Section 1.3	“The EAG has suggested exploratory scenario analyses using discontinuation rates informed by various sources – MANDARA DB (***%), MANDARA OLE (*%).”	Please amend the confidentiality highlighting as follows: “The EAG has suggested exploratory scenario analyses using discontinuation rates informed by various sources – MANDARA DB (***%), MANDARA OLE (*%).”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 16, Section 1.3	“A lower discontinuation rate of ***% is expected to increase the ICER by around £2000/QALY”	Please amend the confidentiality highlighting as follows: “A lower discontinuation rate of ***% is expected to increase the ICER by around £2000/QALY”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 16, Section 1.3	“A higher discontinuation rate, say *% is expected to decrease the ICER by around £2000/QALY.”	Please amend the confidentiality highlighting as follows: “A higher discontinuation rate, say *% is expected to decrease the ICER by around £2000/QALY.”	The EAG accepted the proposed changes from the company and the format in the report was changed.
Page 34, Section 2.2	“The CS highlights the CRPD dataset which reports only **** patients (***%) had rituximab	Please amend the confidentiality highlighting as follows:	The EAG have made the proposed amendment.

	and ** patients (**%) had cyclophosphamide.”	“The CS highlights the CRPD dataset which reports only **** patients (1.0%) had rituximab and *** patients (2.7%) had cyclophosphamide.”	
Page 48, Section 3.2.1, Table 3.3, row 3	“During the trial 140 participants were randomised from 50 sites across the USA (****), Canada (****), Japan (****), Belgium (****), France (****), Germany (****), Israel (****), Italy (****), and the UK (****).”	Please amend the confidentiality highlighting as follows: “During the trial 140 participants were randomised from 50 sites across the USA (****), Canada (****), Japan (****), Belgium (****), France (****), Germany (****), Israel (****), Italy (****), and the UK (****).”	This information is publicly available in the supplementary appendix of Wechsler et al. (2024).{Wechsler, 2024 #30} pages 3 and 4. As the correct reference is used, no changes are needed. We have referenced the supplementary appendix {Wechsler, 2024 #115} in the reference specifically here for clarity.
Page 49, Section 3.2.1, Table 3.3, row 7	“From 140 patients randomised, ** were from four sites across the UK; (**** patients were randomised to benralizumab; ** patients to mepolizumab).”	Please amend the confidentiality highlighting as follows: “From 140 patients randomised, ** were from four sites across the UK; (**** patients were randomised to benralizumab; ** patients to mepolizumab).”	The '18' is not CIC as it's available in the Supplementary Appendix of Wechlser et al. (2024).{Wechsler, 2024 #30} This referenced has been added. The other suggested amendments have been implemented.

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Page 54, Section 3.2.1.1	***** ***** ***** ***** ***** (further discussed in section Error! Reference source not found.). ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** *****	Please remove confidentiality highlighting.	The confidentiality highlighting has now been removed.
Page 55, Section 3.2.1.2	“While differing prescribing practices across treatment sites may account for some of the observed variation, the EAG agree the small sample sizes across sites (London: n=; Cambridge: n=; Leicestershire: n=; Portsmouth: n=) prevent	Please amend the confidentiality highlighting as follows: “While differing prescribing practices across treatment sites may account for some of the observed variation, the EAG agree the small sample sizes	This additional confidentiality marking has now been added.

	any inferences from being made.”	across sites (London: n=█; Cambridge: n=█; Leicestershire: n=█; Portsmouth: n=█) prevent any inferences from being made.”	
Page 64, Section 3.3.1, Table 3.7, row 3	“Patients from the UK only comprised █% of the MANDARA trial population”	Please amend the confidentiality highlighting as follows: “Patients from the UK only comprised █% of the MANDARA trial population”	This information is publicly available in the supplementary appendix of Wechsler et al. (2024),{Wechsler, 2024 #30} pages 3 and 4. As the correct reference is used, no changes are needed.
Page 66, Section 3.3.1.2	“Similarly in the MANDARA trial █% (████) of patients were based in UK across a total of four sites. The remaining MANDARA study population were based in North America (████), Belgium (██), France (██), Germany (██), Italy (██), Israel (██), and Japan (██).”	Please amend the confidentiality highlighting as follows: “Similarly in the MANDARA trial █% (████) of patients were based in UK across a total of four sites. The remaining MANDARA study population were based in North America (████), Belgium (██), France (██), Germany (██), Italy (██), Israel (██), and Japan (██).”	This information is derived from publicly available data in the supplementary appendix of the main trial paper (pages 3 and 4):{Wechsler, 2024 #115} Confidentially marking has now been added and a reference for Document B.
Page 66, Section 3.3.1.3	Furthermore, as described in Section 3.3.1.2, study locations were overall similar; both trials	Please amend the confidentiality highlighting as follows:	This additional confidentiality marking has now been added.

	included a comparable number of patients from the UK (~10- ██ %).	Furthermore, as described in Section 3.3.1.2, study locations were overall similar; both trials included a comparable number of patients from the UK (~10- ██ %).	
Page 67, Section 3.3.1.3	Of note, MIRRA also enrolled patients in Spain, and MANDARA also enrolled patients in Israel and there was a markedly higher proportion of patients from North America in MIRRA than the MANDARA trial (~48% vs ██ %).	Please amend the confidentiality highlighting as follows: Of note, MIRRA also enrolled patients in Spain, and MANDARA also enrolled patients in Israel and there was a markedly higher proportion of patients from North America in MIRRA than the MANDARA trial (~48% vs ██ %).	This additional confidentiality marking has now been added.
Page 68, Section 3.3.1.4	Additionally, treatment with benralizumab was estimated to have a ██ % lower risk of relapse over the course of the year compared to SoC	Please amend the confidentiality highlighting as follows: Additionally, treatment with benralizumab was estimated to have a ██ % lower risk of relapse over the course of the year compared to SoC	This additional confidentiality marking has now been added.
Page 80, Section 4.2.1	“The company used a ██ % per year in the economic model as a conservative assumption,	“The company used a ██ % per year in the economic model as a conservative assumption,	This additional confidentiality marking has now been added.

	validated by clinical experts to be reflective of UK clinical practice”	validated by clinical experts to be reflective of UK clinical practice”	
Page 83, Section 4.2.2.2	“However, the company considered AEs related to OCS use in the economic model. CPRD analysis conducted by the company on people with EGPA in England revealed that OCS were prescribed for ****% of people on the OCS treatment over a mean follow-up of 5.4 years post-diagnosis.”	Please amend the confidentiality highlighting as follows: “However, the company considered AEs related to OCS use in the economic model. CPRD analysis conducted by the company on people with EGPA in England revealed that OCS were prescribed for 86.2% of people on the OCS treatment over a mean follow-up of 5.4 years post-diagnosis.”	This additional confidentiality marking has now been removed.
Page 91, Section 4.2.4.1	“The company makes the assumption that the percentage of stable patients who are refractory reduces from ****% to ****% after one year and then it remains constant”	“The company makes the assumption that the percentage of stable patients who are refractory reduces from ****% to ****% after one year and then it remains constant”	This additional confidentiality marking has now been added.
Page 93, Section 4.2.6, Table 4.7, row 3	“* out of 177 participants were children below the age of 18 years, who participated completing the EQ-5D-5L questionnaire, which may not be	Please amend the confidentiality highlighting as follows: “* out of 177 participants were children below the age of 18 years, who participated	As per Issue 2, the EAG agrees with the suggested recommendation. This point has therefore been removed from the text.

	a suitable instrument for measuring quality of life in children and young adults.”	completing the EQ-5D-5L questionnaire, which may not be a suitable instrument for measuring quality of life in children and young adults.”	
Page 94, Section 4.2.6.1	“Out of 177 patients, *** patients in the Adelphi DSP study suffered from various organ damage”	“Out of 177 patients, *** patients in the Adelphi DSP study suffered from various organ damage”	This additional confidentiality marking has now been added.
Page 94, Section 4.2.6.1	“The Adelphi DSP study: The study was conducted among 177 EGPA patients from UK (█), Germany (█), France (█), Italy (█), Spain (█) US (█). A sample size of █ was reflected the UK clinical practice because of the low incidence of the disease.”	Please amend the confidentiality highlighting as follows: “The Adelphi DSP study: The study was conducted among 177 EGPA patients from UK (█), Germany (█), France (█), Italy (█), Spain (█) US (█). A sample size of █ was reflected the UK clinical practice because of the low incidence of the disease.”	This additional confidentiality marking has now been added.
Page 95, Section 4.2.6	“**** out of the 177 patients were below 18 years of age and the minimum age included in the study was █ years.”	Please amend the confidentiality highlighting as follows: “**** out of the 177 patients were below 18 years of age and the minimum age included in the study was █ years.”	This additional confidentiality marking has now been added.

Page 95, Section 4.2.6.1, Table 4.8, rows 1–3	***** ***** *****	Please amend the confidentiality highlighting as follows: ***** ***** *****	This additional confidentiality marking has now been added.
Page 95, Section 4.2.6.1, Table 4.9, rows 1–13	***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** *****	Please amend the confidentiality highlighting as follows: ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** ***** *****	This additional confidentiality marking has now been added.

Page 97, Section 4.2.7, Table 4.12, row 3	“The rate of treatment discontinuation of benralizumab (****%) was unusually low in the MANDRARA DB trial when compared to that observed in the real world. Alternative sources showed discontinuation rates ranging from ****% for benralizumab treatment. The company assumed a ***% discontinuation rate, adopting a conservative approach in the model. To explore the possible effects of a higher treatment discontinuation rate on the incremental cost-effectiveness, a scenario of % discontinuation rate was explored in the model.”	Please amend the confidentiality highlighting as follows: “The rate of treatment discontinuation of benralizumab (****%) was unusually low in the MANDRARA DB trial when compared to that observed in the real world. Alternative sources showed discontinuation rates ranging from ****% for benralizumab treatment. The company assumed a ***% discontinuation rate, adopting a conservative approach in the model. To explore the possible effects of a higher treatment discontinuation rate on the incremental cost-effectiveness, a scenario of % discontinuation rate was explored in the model.”	This additional confidentiality marking has now been added.
Page 99, Section 4.2.7.1	“much higher than the trial period data. In patients with severe asthma, benralizumab discontinuation rate was 11.8%. The company conservatively assumed a discontinuation rate	Please amend the confidentiality highlighting as follows: “much higher than the trial period data. In patients with severe asthma, benralizumab discontinuation rate was 11.8%. The company conservatively	This additional confidentiality marking has now been added.

	of █% and explored a scenario with █%.”	assumed a discontinuation rate of █% and explored a scenario with █%.”	
Page 100, Section 4.2.7.1	“The change in average dose over time in Figure 7 suggests that ** ***** ***** ***** ***** ***** ***** *	Please amend the confidentiality highlighting as follows: “The change in average dose over time in Figure 7 suggests that ** ***** ***** ***** ***** ***** ***** *	This additional confidentiality marking has now been added.
Page 122, Section 6.1.1.2	“The OCS discontinuation rate in the benralizumab arm was assumed to be █% per year. The EAG considers it quite possible that the OCS discontinuation rate will decline over time. In the EAG base case the discontinuation rate is assumed to decline linearly from █% at year 1 to 0% at year 5”	Please amend the confidentiality highlighting as follows: “The OCS discontinuation rate in the benralizumab arm was assumed to be █% per year. The EAG considers it quite possible that the OCS discontinuation rate will decline over time. In the EAG base case the discontinuation rate is assumed to decline linearly from █% at year 1 to 0% at year 5”	This additional confidentiality marking has now been added.

Section 5: Scenario implementation in the model

Whilst reviewing the EAG models shared, the Company has identified some instances where the implementation of scenarios in the models was partially incorrect – these are summarised below.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 142, Section 6.2.5 Table 6.11	When implementing “RR of SoC with OCS vs SOC without OCS = 2” – this is only applied to the benralizumab arm in the model, not the SoC arm of the model. By replicating this assumption in the SoC arm of the model, the ICER decreases from £32,420 to £31,480	Incorrect implementation in model	The RR of SoC with OCS vs SOC without OCS = 2 was intentionally only applied to the benralizumab arm of the model only. The proportion of patients receiving OCS does not change in the OCS arm of the model over time. Consequently, only the transition probabilities in the benralizumab arm of the model need to be adjusted, and this is done so using a weighted average and accounting for the initial proportion of patients receiving OCS. This is described in the equation in the appendix of the EAG report.
Page 142, Section 6.2.5 Table 6.11	When implementing “RR of SoC with OCS vs SOC without OCS = 4” – this is	Incorrect implementation in model	The RR of SoC with OCS vs SOC without OCS = 4 was

	only applied to the benralizumab arm in the model, not the SoC arm of the model. By replicating this assumption in the SoC arm of the model, the ICER decreases from £33,012 to £31,787		intentionally only applied to the benralizumab arm of the model only. The proportion of patients receiving OCS does not change in the OCS arm of the model over time. Consequently, only the transition probabilities in the benralizumab arm of the model need to be adjusted, and this is done so using a weighted average and accounting for the initial proportion of patients receiving OCS. This is described in the equation in the appendix of the EAG report.
Page 142, Section 6.2.5 Table 6.11	When implementing “RR of SoC with OCS vs SOC without OCS = 8” – this is only applied to the benralizumab arm in the model, not the SoC arm of the model. By replicating this assumption in the SoC arm of the model, the ICER decreases `	Incorrect implementation in model	The RR of SoC with OCS vs SOC without OCS = 8 was intentionally only applied to the benralizumab arm of the model only. The proportion of patients receiving OCS does not change in the OCS arm of the model over time. Consequently, only the transition probabilities in the benralizumab arm of the model need to be adjusted,

			and this is done so using a weighted average and accounting for the initial proportion of patients receiving OCS. This is described in the equation in the appendix of the EAG report.
Page 142, Section 6.2.5 Table 6.11	When implementing “All of those who discontinue OCS do not discontinue benralizumab” – these patients are categorised as “responders” but have been allocated the efficacy of “all benralizumab patients” – not the efficacy of responders (by applying the incorrect transition matrix). This approach under-estimates the long-term benefit. See Figure 2 in Appendix. By applying the “responder” transition matrix to these patients in the model, the ICER decreases from £38,521 to £33,388	Incorrect implementation in model.	The EAG made amendments in the model and provided the results in Table 6.11. The text on page 145, Section 6.3 has been edited to read: “Scenarios 6 and 12 affect the ICER the most by only a fraction because benralizumab discontinuation is also reduced in the scenario as well as increasing the percentage of patients who receive OCS while receiving SoC.” In addition, the results for the Scenarios 12 and 13

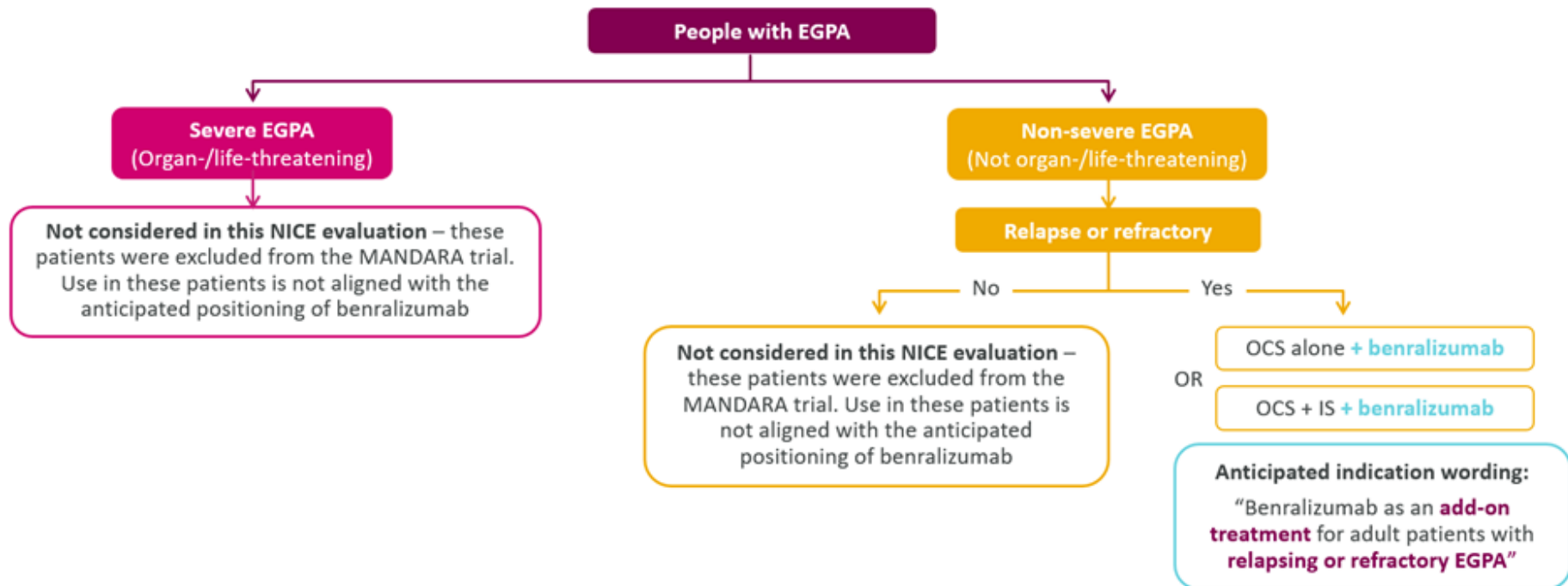
			have been updated in Table 6.11 and the results for scenarios 6,12,13 updated in Table 1.8 updated.

Appendix

Proposed positioning of benralizumab

Error! Not a valid bookmark self-reference. (Figure 5 in CS) presents the proposed positioning for benralizumab as an add-on treatment for adult patients with relapsing or refractory EGPA who are receiving OCS with or without stable IS therapy, as validated by clinical experts.

Figure 1: Potential future clinical care pathway for patients with EGPA



Implementation of EAG exploratory Scenario 6

On page 129, Section 6.1.2.2, the EAG report states that “Scenario (6) assumes that patients who discontinue OCS while on benralizumab do so because they are responders, and they do not subsequently discontinue benralizumab.”.

However, the EAG allocated these patients the transition matrix of all patients in the benralizumab arm prior to the time of response assessment. Given that these patients are responders, they should be allocated the transition matrix derived from patients who respond to the treatment (responder transition matrix) – see Figure 2 below.

Figure 2: Illustration of EAG exploratory Scenario 6

Patient starts on benralizumab + OCS*

Patient discontinues OCS (responder)

Benralizumab + OCS*

Benralizumab only

In the EAG exploratory scenario 6, these patients are allocated the transition matrix of “pre-response assessment”; however, these are responders and should be allocated the “responder” transition matrix

*NB: This patient is also on +/- immunosuppressants, but for the purpose of simplicity this has been omitted from the figure

Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort

The table included in the EAG report is displayed below.

Table 1: Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort (Table 4.6 of EAG report)

OCS discontinuation rate	T2DM	eCVD	OP	T2DM/ eCVD	T2DM/ OP	eCVD/ OP	T2DM/ eCVD/ OP
37.96% per year	59.3	83.6	57.4	63.1	31.7	34.6	24.1
0% per year	61.7	82.3	50.7	48.9	23.7	24.4	20.9
37.96% first year, 0% subsequently	61.2	83.0	52.7	52.8	25.8	27.0	21.7

When comparing with the models provided by the EAG, the Company identified some discrepancies in the figures listed in Table 1 above. Table 2 below shows the proportions derived from the EAG model.

Table 2: Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort (revised numbers which Company can find from EAG model)

OCS discontinuation rate	T2DM	eCVD	OP	T2DM/ eCVD	T2DM/ OP	eCVD/ OP	T2DM/ eCVD/ OP
37.96% per year	61.2	81.8	50.6	48.9	23.7	24.4	20.8
0% per year	58.7	83.0	57.2	63.2	31.9	34.8	24.1
37.96% first year, 0% subsequently	60.7	82.5	52.7	53.2	26.0	27.3	21.7

Table 3: Predicted numbers of patients with combinations of chronic OCS events after 20 years per 1000 initial cohort (revised numbers the EAG have used in the edited report)

OCS discontinuation rate	T2DM	eCVD	OP	T2DM/ eCVD	T2DM/ OP	eCVD/ OP	T2DM/ eCVD/ OP
37.96% per year	61.2	81.8	50.6	48.9	23.7	24.4	20.8
0% per year	58.7	83.0	57.2	63.2	31.9	34.8	24.1
37.96% first year, 0% subsequently	60.8	82.4	52.5	52.8	25.8	27.0	21.6
Source: EAG base-case Excel Model							

The EAG made the amendments in Table 4.6 in the report.