Benralizumab *for* treating severe eosinophilic asthma: NICE single technology appraisal

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Background

- Eosinophilic asthma is a subtype of severe asthma characterized by the higher than normal presence of eosinophils (proinflammatory white blood cells) in the lung and sputum.
- Patients with eosinophilic asthma are at a higher risk of exacerbations (asthma attacks).
- In these patients, continuous use of oral corticosteroids (OCS) may be required to prevent exacerbations. When taken frequently or long-term, these can cause major side effects.
- Recent studies have shown that monoclonal antibodies can reduce asthma exacerbations, and improve health-related quality of life and lung function.
- AstraZeneca, the manufacturer of a monoclonal antibody benralizumab (Fasenra®), submitted evidence on the clinical and cost-effectiveness of this drug, in combination with standard of care (SOC), for adults with severe asthma with elevated blood eosinophils, as part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal process [1].
- The Peninsula Technology Assessment Group (PenTAG) was commissioned to act as the Evidence Review Group (ERG) in this appraisal.

Objectives

- To critically review submitted evidence.
- To conduct additional analyses regarded by the ERG as most relevant to the NHS in England [1].

Methods

- **Treatment**:
  Benralizumab plus standard of care (BEN + SOC)
  BEN: 30 mg every 4 weeks for the first 3 doses then every 8 weeks
- **Comparators**:
  - mepolizumab (MEPO) + SOC
  - reslizumab (RESLI) + SOC
  - SOC alone
- **Patient populations considered in this study**:

Comparator	*Population*
MEPO + SOC	MEPO-eligible population[1]
RESLI + SOC	RESLI-eligible population[2]
SOC	A subgroup from pooled SIROCCO and CALIMA RCTs [2, 3][3]

Key: RCT, randomized control trial

[1] *Adults with the blood eosinophil count of ≥300 cells/μL in the previous 12 months and ≥4 asthma exacerbations needing systemic corticosteroids in the previous 12 months or continuous use of OCS of at least the equivalent of prednisolone 5 mg/day over the previous 6 months (NICE technology appraisal guidance [TA431]).*

[2] *Adults with inadequately controlled asthma despite maintenance therapy with high-dose inhaled corticosteroids (ICS) plus another drug, only if the blood eosinophil count has been recorded as ≥400 cells/μL and the person has had ≥3 severe asthma exacerbations needing systemic corticosteroids in the past 12 months (NICE technology appraisal guidance [TA479]).*

[3] *Adults with an eosinophil count between 300 to 399 cells/μL, who have had exactly 3 exacerbations and are not taking OCS (patient population for whom SOC is the only treatment option, considered by the company in an additional analysis on request from NICE)*

- **Major outcomes**:
  - Reduction in annual asthma exacerbations
  - Reduction in oral corticosteroid (OCS) dose
  - Quality of life
- **Clinical effectiveness evidence:**

Comparator	*Source*
MEPO + SOC	Matched-adjusted indirect comparison (MAIC)
RESLI + SOC	No evidence
SOC	Pooled SIROCCO/CALIMA, and ZONDA RCTs [2-4]

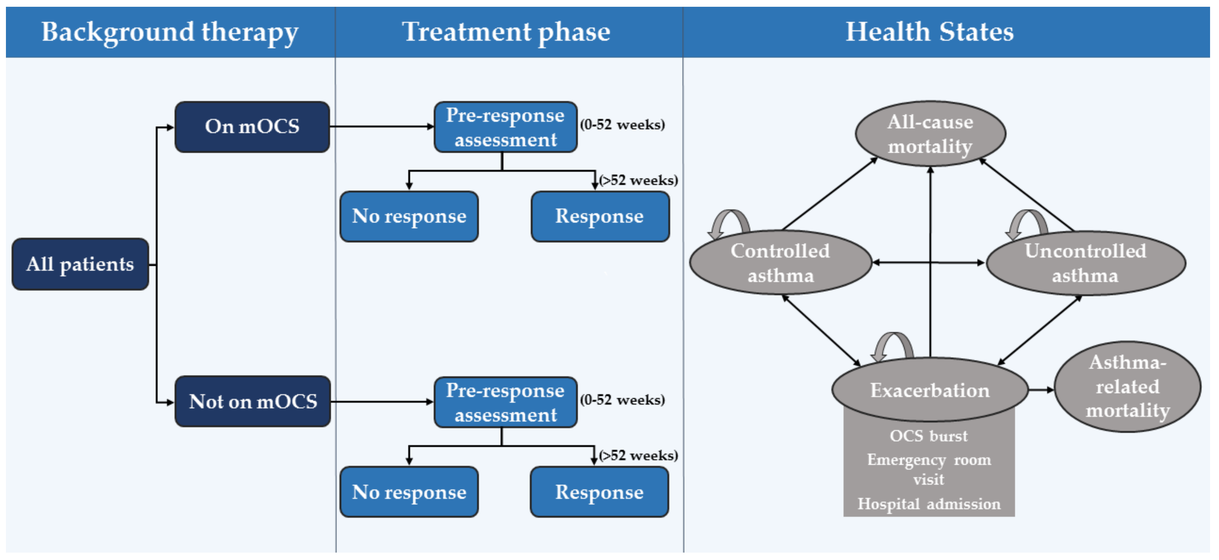
- **Quality of life evidence:**

Measure	*Source*
EQ-5D-5L	Pooled SIROCCO/CALIMA, and ZONDA RCTs [2-4]
AQLQ(S)+12	ZONDA [4]

Note: Both measures were mapped onto EQ-5D-3L.

- **Model type**: Markov
- **Perspective:** National Health Service (NHS) and Personal Social Services (PSS)
- **Discount rate:** 3.5%/year

Markov model



Key: mOCS, maintenance oral corticosteroids

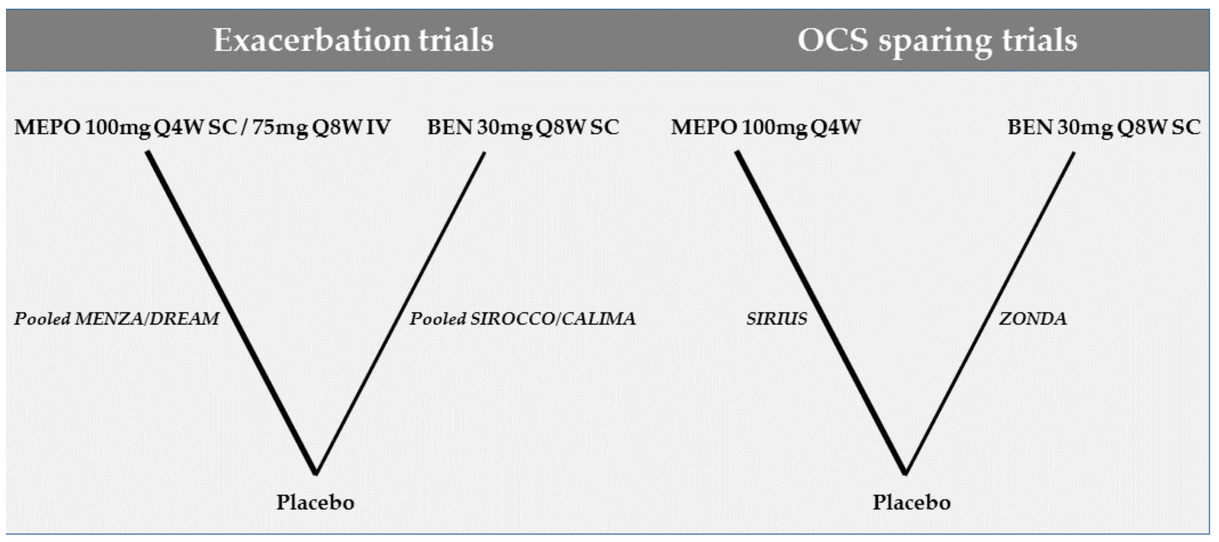
- In the model, patients are separated into two groups, based on whether they are currently taking mOCS.
- Add-on treatment is continued for the duration of the pre-response assessment period (52 weeks, based on CALIMA and SIROCCO trials) [2, 3].
- At 52 weeks, patients who have not responded to treatment are reverted back to SOC, while the responders continue to receive add-on biologic for life.
- At the beginning of treatment, all patients are assumed to start in a state of uncontrolled asthma (which was in line with the inclusion criteria in SIROCCO and CALIMA).
- At the end of each model cycle, patients can move to the other health states as depicted by arrows.
- An exacerbation was assumed to last for 8 weeks (determined by visual inspection from pooled SIROCCO/CALIMA utility data as the length of time taken for utility to return to pre-exacerbation level).
- Mean age of patients at baseline: 50 years
- Model cycle: 2 weeks
- Time horizon: Lifetime

Matched-adjusted indirect comparison (MAIC)

MAIC analysis for BEN vs. MEPO

- Anchored MAIC analysis was conducted to compare the treatment effects of BEN and MEPO.
- The comparison was performed in the full trial populations (not in the subgroup for which NICE recommendation was sought). This was a limitation of the study.
- In the base-case MAIC:
  - data from SIROCCO and CALIMA RCTs (for BEN vs. placebo), and MENSA and DREAM RCTs (for MEPO vs. placebo) were used for exacerbation analysis,
  - data for OCS-sparing was derived from ZONDA RCT (BEN) and SIRIUS RCT (MEPO) [2-7].
- *The results of the MAIC analyis for BEN vs. MEPO are confidential.*

Evidence network for comparison of BEN vs. MEPO:



Key: IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

MAIC analysis for BEN vs. RESLI

- A MAIC was not feasible due to significant differences in baseline characteristics in BEN and RESLI trials.
- Therefore, *equivalent efficacy of BEN and RESLI was assumed in the economic analysis* [1].

Subgroup analysis from pooled SIROCCO and CALIMA RCTs

Based on the analysis of the SIROCCO and CALIMA trials, BEN was found to be more efficacious in patients with blood eosinophils ≥300 cells/μL and ≥3 exacerbations in the previous year, who have failed on high-dose inhaled corticosteroid (ICS) plus long-acting beta agonist (LABA) therapy.

Estimate, 95% CI	*BEN 30mg Q8W (N=123)*	*Placebo (N=136)*
Marginal annual exacerbation rate	0.85 (0.63, 1.15)	1.83 (1.45, 2.30)
Rate ratio	0.47 (0.32, 0.67)	
P value	<0.001	
Annual exacerbation rate associated with ER visit	0.05 (0.02, 0.12)	0.15 (0.08, 0.30)
Rate ratio	0.31 (0.09, 1.01)	
P value	0.051	
Annual exacerbation rate associated with hospitalisation: rate ratio	1.01 (0.30, 3.45)	
P value	0.988	

Results

ICERs under PAS prices for BEN, MEPO and RESLI (£ per QALY gained)

Comparison	*Company*	*ERG*
BEN vs. MEPO	N/A	<£20,000
BEN vs. RESLI	N/A	BEN is cost saving
BEN vs. SOC	£38,304	£45,406

Key: CiC, commercial in confidence; ICER, incremental cost-effectiveness ratio; N/A, not applicable (AstraZeneca did not conduct this analysis); PAS, patient access scheme; QALY, quality-adjusted life-year
Note: The PAS prices for all the treatments are CiC.
Sensitivity analyses produced qualitatively similar results.

Major drivers of the difference in the company's and ERG's estimates

- Rates of asthma-related mortality
- Proportions of patients using mOCS at baseline

NICE's End-of-Life (EoL) criteria

BEN is unlikely to meet the EoL criteria [8].

Conclusions

BEN was recommended by NICE in people with severe asthma eligible either for MEPO or RESLI only if the company provides it according to the commercial arrangement (NICE technology appraisal guidance [TA565] [1]):

- If BEN, MEPO or RESLI are equally suitable, start treatment with the least expensive option (taking into account drug and administration costs).
- At 12 months:
  - stop treatment if the asthma has not responded adequately or
  - continue treatment if the asthma has responded adequately

and assess response each year.

An adequate response is defined as:

- *a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or*
- *a clinically significant reduction in continuous oral-corticosteroid use while maintaining or improving asthma control.*

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Further information

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