Lead team presentation
Benralizumab for treating inadequately controlled asthma

Background and Clinical Effectiveness

1st Appraisal Committee meeting (17 April 2018)

Committee A

Lead team: Rita Faria, Rachel Hobson, Sarah Parry, Pamela Rees

Assessment Group: Peninsula technology Assessment Group (PenTAG)

NICE technical team: Sana Khan, Eleanor Donegan

For public observers

Key decision points 1

- Where does benralizumab fit in the clinical pathway? Are there any particular advantages of benralizumab over other available treatments?
- The company have made a case for a **blended subgroup** of patients with 3+ exacerbations in the previous 12 months **OR** on maintenance oral corticosteroids (mOCS) for the previous 6 months. Should the groups based on mOCS use be considered separately?
- Is the most relevant comparator standard of care (company) or mepolizumab (ERG)?
- Is benralizumab clinically effective compared with standard of care?
  - Is the treatment effect likely to differ depending on previous annual exacerbation rate and/or by use of maintenance oral corticosteroids?
  - Is clinical equivalence of benralizumab and reslizumab reasonable to assume given different modes of action? The ERG considered this to be a strong assumption.

Key decision points 2

- The matched adjusted indirect comparison (MAIC) comparing benralizumab with mepolizumab was conducted in the intention to treat (ITT) population. Mepolizumab is recommended by NICE in patients with 4+ exacerbations in the previous 12 months or on mOCS in the previous 6 months.
  - Does the committee consider that the comparison with benralizumab can be conducted in the subgroup with 3+ exacerbations population or should it be restricted to patients with 4+ exacerbations?
  - Are the ITT MAIC results also applicable to the proposed subgroup?
- Is the MAIC of benralizumab compared with mepolizumab robust? Are any differences clinically meaningful?
- Sensitivity analysis including MUSCA (24 week HRQOL trial) in the MAIC trial showed no significant difference between benralizumab and mepolizumab (numerically favoured mepolizumab). Should MUCSA be included in the MAIC?
- The implication of the company approach is that benralizumab is more effective than mepolizumab but the same as reslizumab, does this imply that resilzumab is more effective than mepolizumab, and is this supported by evidence?

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Disease Background

- Asthma is a disease of airways with symptoms such as breathlessness, chest tightness, wheezing and cough
- 4.8 million people in England & Wales have asthma and in 2015 there were 1,468 asthma related deaths in the UK, which is the highest level for over 10 years
- 5-10% people have severe asthma defined as:
  - 'asthma that requires treatment with high dose inhaled corticosteroids plus a second controller medicine to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy' (NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and guidelines from the Global Initiative for Asthma 2017 (GINA)
- Eosinophilic asthma is now recognized as an important subtype of asthma based on the pattern of inflammatory cellular infiltration in the airway. It can be associated with increased asthma severity, allergy, late-onset disease, and steroid resistance
- Severe asthma initially treated with inhaled corticosteroids (IHS) AND either oral corticosteroids (OCS) or monoclonal antibodies (omalizumab, mepolizumab or reslizumab) later in the clinical pathway in the NHS

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Previous appraisals

- Biologics recommended by NICE for treating severe eosinophilic asthma:
  - **NICE TA431** (2017) recommends **mepolizumab** in adults with a blood eosinophil count of **300 cells/microlitre** or more in the previous 12 months, **and** who have had **4 or more asthma exacerbations** needing systemic corticosteroids in the previous 12 months **or** has had continuous oral corticosteroids over the previous 6 months
  - **NICE TA479** (2017) recommends **reslizumab** in adults who have had a blood eosinophil count recorded as **400 cells/microlitre or more and** who have had **3 or more severe asthma exacerbations** needing systemic corticosteroids in the past 12 months
- **NICE TA278** (2013) recommends omalizumab for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)
  - Omalizumab is used in a specific form of asthma (IgE mediated) (TA479) and was not in the final scope

NOTE: Biologic therapies not included in NG80 but covered in updated GINA 2017 guidelines

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Patient perspective (Asthma UK)

- Life with severe asthma is limiting
- The impact of caring for someone with severe asthma is substantial
- People with severe eosinophilic asthma do not respond to standard treatment and require more intensive treatments to control symptoms, prevent attacks, hospitalisations and deaths
- Substantial unmet need for people with severe asthma. Treatment options include high doses of drugs with very poor side effect profiles.
- The side effects and ineffectiveness at reducing severe asthma symptoms are significant contributors to low adherence rates.
- Biologics recommended by NICE have been life-transforming for people with severe asthma but are limited to a specific sub-population.
- Benralizumab could provide an alternative option for people with severe eosinophilic asthma who do not respond well to existing treatment options, in that their symptoms persist and their asthma remains uncontrolled

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Expert Comments (BTS/RCP)

- Benralizumab would allow an additional biologic option besides OCS to become available to patients
- Biologic therapy is given following assessment by specialist centres when current treatment has been optimised and compliance assessed. Centres will have been approved through NHSE specialist commissioning
- Benralizumab is innovative due to its different mode of action on the IL-5 receptor although the effect of reducing eosinophils is not unique
- The clinical expert statement:
  - Many patients on mOCS are poorly controlled
  - 0.5 or more improvement in ACQ, 30% reduction in AER requiring systemic steroids or 50% reduction in maintenance systemic steroids is clinically meaningful
  - Il-5 antagonists are a step-change, similar benefits for benralizumab/mepolizumab/resilizumab

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Burden of OCS use (company submission)

- Approximately 40% of people with severe asthma regularly use OCS
- Frequent or chronic use of OCS in asthma associated with short-term and long-term detrimental side effects including osteoporosis, peptic ulcers, cataracts, adrenal suppression, weight gain, hypertension, mood problems, high blood pressure, and type 2 diabetes
- A study using Clinical Practice Research Datalink (CPRD) linked with Hospital episode statistics data and Optimum Patient Care Research Database (OPCRD) was conducted by the company
  - [redacted]
  - [redacted]
  - [redacted]

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Details of the technology

Technology	Benralizumab
Marketing authorisation	Add-on maintenance for severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists (LABA) European marketing authorisation granted in January 2018
Mechanism of action	Binds through interleukin (IL)-5Rα and inhibits IL-5 which reduces eosinophil numbers and activity. Different mode of action than other anti-IL-5 antibody (mepolizumab, reslizumab), which results in eosinophil reduction, but not depletion.
Administration	30 mg dose every 4 weeks for first 3 doses, then 8 weekly as subcutaneous injection (accessorised pre-filled syringe)
Acquisition cost	List price: £1955/vial (30 mg SC injection) PAS price: £[redacted] (30 mg SC injection)

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	NICE Final scope	Company Decision Problem
Population	Adults with severe asthma with elevated blood eosinophils	Adults with severe eosinophilic asthma inadequately controlled despite high-dose ICS and LABA+ blood eosinophil count of ≥300 cells/µl AND either 3 or more asthma exacerbations needing systemic steroids in past 12 months OR treatment with continuous OCS in previous 6 months. Company –maximum clinical benefit based on the trial data ERG are in agreement
Intervention	Benralizumab as an add-on to optimised standard therapy (OST)	As per scope
Comparators	• optimised standard therapy • reslizumab (in addition to OST) • mepolizumab (in addition to OST)	As per scope Company considered standard of care (SoC) main comparator ERG - mepolizumab more appropriate

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Benralizumab clinical studies (1)

Study	Population (ITT)	Intervention	Comparator
SIROCCO (n=1205) **24/374 UK centres**	• 12–75 years with uncontrolled asthma: • **high dose** ICS + LABA, • **2+ exacerbations** prior year, • Blood eosinophil ≥300/µL (N.B. high dose ≥ **800µg** FP)	30 mg SC injection for 48 wks: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 4 (with placebo injection at the 4W interim)	Placebo Q4W
CALIMA (n=1306) **No UK centres**	• 12–75 years with uncontrolled asthma • **medium to high dose*** ICS + LABA • **2 or more asthma exacerbations** • blood eosinophil ≥300/µL N.B n=215 (16%) received medium-dose ICS (**500µg** FP daily) + LABA BUT were NOT included in any analyses.	30 mg subcutaneous injection for 56 weeks of either: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 5 (with placebo injection in interim)	

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Benralizumab clinical studies (2)

Study	Outcomes	Pre-defined subgroups
SIROCCO (n=1205)	**Primary outcome:** Annual asthma exacerbation rate (AER) **Secondary outcomes:** • (FEV1) • Total asthma symptom score - week 48 • health related quality of life (HRQoL) • healthcare resource use utilisation • adverse events	• Baseline OCS use (yes/no) • Gender • Age (<18, 18–<65, or ≥65 yrs) • Geographic region • Number of exacerbations in previous year (2, 3, or ≥4). • Race
CALIMA (n=1306)	**Primary outcome:** Annual asthma exacerbation rate ratio versus placebo **Secondary outcomes:** • Total asthma symptom score -week 56 • Rest as above for SIROCCO	

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Benralizumab clinical studies (3)

Study	Population (ITT)	Intervention	Comparator
ZONDA (n=220) **No UK centres**	• 18–75 years with uncontrolled asthma • **high-dose** ICS + LABA, history • **1 or more asthma exacerbations** • **blood eosinophils ≥150/µL**	30 mg subcutaneous injection for 28 weeks of either: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 2	Placebo Q4W
	Primary outcome: **%** reduction in oral glucocorticoid dose to week 28 **Secondary outcomes:** • reduction in average daily OCS of ≥25%, ≥ 50% or ≥100% • Discontinuation of OCS use • As above for SIROCCO & CALIMA	• Age • Gender • Body mass index • Number of exacerbations in the previous year • Geographical region • OCS dose at baseline • Blood eosinophil levels	

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Clinical effectiveness ITT results

SIROCCO	Placebo	Benralizumab 30 mg Q8W
Primary endpoint: Annual asthma exacerbation rate over 48 weeks		
Number of patients	267	267
Rate estimate (95% CI)	1.33 (1.12–1.58)	0.65 (0.53–0.80)
Absolute difference estimate (95% CI)	-	−0.68 (−0.95- −0.42)
Rate ratio *vs* placebo (95% CI)	-	0.49 (0.37–0.64)
CALIMA	**Placebo**	**Benralizumab 30 mg Q8W**
Primary endpoint: Annual asthma exacerbation rate over 56 weeks		
Number of patients	248	239
Rate estimate (95% CI)	0.93 (0.77–1.12)	0.66 (0.54–0.82)
Absolute difference estimate (95% CI)	-	−0.26 (−0.48 to −0.04)
Rate ratio *vs* placebo (95% CI)	-	0.72 (0.54–0.95)

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Clinical effectiveness ITT results: utility scores

SIROCCO	Placebo	Benralizumab 30 mg Q8W
EQ-5D-5L (mapped to EQ-5D-3L from EQ-5D-5L)		
Number of patients analysed*	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference(95% CI)	[redacted]	[redacted]
CALIMA	**Placebo**	**Benralizumab 30 mg Q8W**
EQ-5D-5L (mapped to EQ-5D-3L from EQ-5D-5L)		
Number of patients analysed*	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference (95% CI)	-	[redacted]

*excludes adolescents

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Heterogeneity in regional exacerbation rates between SIROCCO and CALIMA

- Differences in the treatment effect might be due to three key drivers: exacerbation history, regional effect and background medication
- Exacerbation rates during treatment were higher in SIROCCO and the reduction in exacerbation rates with benralizumab was numerically greater.
- Subgroup with ≥3 exacerbations in year before trial were under-represented in Eastern Europe and South America regions in the CALIMA study

  However, the proportion of patients who had ≥ 3 exacerbations in the previous year study were similar in CALIMA (39.4%) and SIROCCO (41.4%).

ERG note similar stratified randomisation implemented in both trials – argument of possible lower baseline exacerbation rates does not hold.

- Possible placebo response in CALIMA as exacerbation rate was 0.93 per year in placebo group during treatment compared with 2.8 seen in the prior year
- CALIMA participants were provided background medication of high dose ICS/LABA for duration of whole trial thereby, increasing the potential for a stronger placebo response.

ERG does not agree – differences between baseline placebo rates and placebo rates at the end of trial were similar in CALIMA (1.87) and SIROCCO (1.77)

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Pooled clinical effectiveness results: SIROCCO and CALIMA

- Patients on medium-dose ICS in CALIMA were excluded
- Data from 1204 patients in SIROCCO and 1091 patients in CALIMA (total of 2295) on high-dose ICS plus LABA showed that benralizumab Q8W reduced the annual rate of exacerbations by 43% compared with placebo (RR = 0.57; 95% CI: 0.47-0.69, p < 0.0001)
- Subgroup analysis of pooled data suggest that exacerbation reduction was dependent on previous exacerbations, baseline blood eosinophil counts, and baseline lung function.
- Higher exacerbation reduction for patients with baseline AER ≥ 3, and also for patients with baseline blood eosinophil counts ≥ 300 cells/μL

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Clinical effectiveness results: pooled SIROCCO/CALIMA subgroup in which NICE recommendation is sought

Estimate, 95% CI	Placebo (N=136)	Benralizumab 30mg Q8W (N=123)
Primary efficacy endpoint: Marginal annual exacerbation rate		
Rate estimate	1.83 (1.45, 2.30)	0.85 (0.63, 1.15)
Marginal absolute difference vs placebo	-	-0.98 (-1.46, -0.50)
Rate ratio	-	0.47 (0.32, 0.67)
P value	-	<0.001
Key secondary endpoints		
ACQ-6 score (decrease in score represents improvement)		
Change from baseline	-1.16	-1.59
Estimate for difference vs placebo	-	-0.43 (-0.69, -0.16)
P value	-	0.002
Mean EQ-5D-5L score		
Change from baseline	0.06 (0.04, 0.09)	0.10 (0.08, 0.13)
Estimate for difference vs placebo	-	0.04 (0.01, 0.08)
P value	-	0.019

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Subgroup analysis of ZONDA: blood eosinophil level ≥ 300 cells/µL

[redacted]

Estimate, 95% CI	Benralizumab 30mg Q8W (N=61)	Placebo (N=64)
Percent reduction in OCS dose, median (95% CI)	75.00 (60.00, 91.70)	0.00 (0.00, 28.60
Comparison (difference between medians)		
Eligible patients with 100% reduction from baseline in final OCS dose	[redacted]	[redacted]
Comparison (difference between medians)	[redacted]	
Annual exacerbation rate	[redacted]	[redacted]
Comparison (rate ratio)	[redacted]	
AQLQ(S)+12 score change from baseline	[redacted]	[redacted]
Comparison (difference in LS means)	[redacted]	

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Comparison with existing biologics

- Network meta-analysis (NMA) ruled out by company
- Anchored matched adjusted indirect comparison (MAIC) chosen to adjust for the cross-trial differences in patient characteristics
- Literature identified effect-modifiers validated by external clinical experts
- The MAIC included:
  - only Phase III trials evaluating approved respiratory biologics in severe uncontrolled asthma on **high-dose** ICS plus at least one additional controller
  - studies evaluating only EMA licensed or US FDA licensed doses of respiratory biologics
- **MAIC only considered feasible for mepolizumab comparison** and in the ITT population because of limited data on the comparator subgroup
  - the relative treatment effect was assumed to also apply to the severe subgroup

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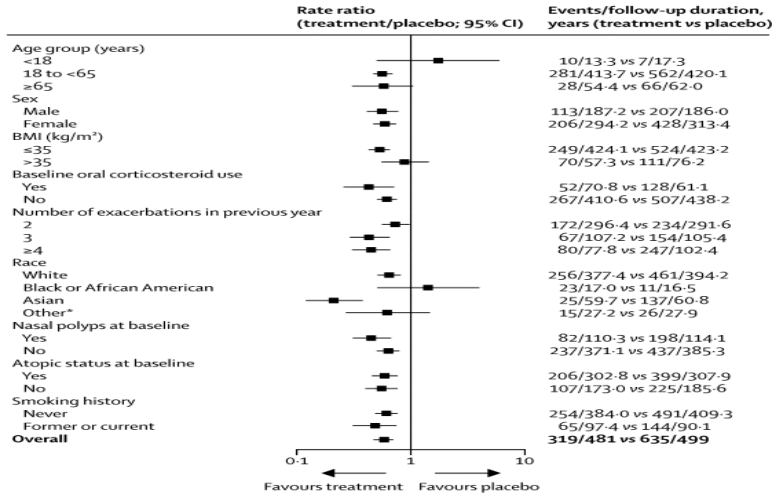
Effect of patient baseline characteristics on the efficacy of benralizumab



Data from ITT population from the high-dosage IHS cohorts from SIROCCO and CALIMA studies (baseline blood eosinophils ≥300 cells per µL; full analysis set, pooled)

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MAIC – benralizumab vs mepolizumab

- 3 benralizumab (SIROCCO, CALIMA, ZONDA) and 3 mepolizumab (MENSA, DREAM,SIRIUS) trials were included in the MAIC analysis
- MUSCA trial not included as the primary objective was HRQoL and study was not powered to detect differences in efficacy outcomes. Study duration was also comparatively shorter (24 weeks) than other trials (SIROCCO: 48 weeks and CALIMA 56 weeks)
  - A sensitivity analysis including this trial conducted instead
- Despite differences between benralizumab and mepolizumab trials e.g. ICS dose, priory history of exacerbation and baseline OCS), the effective sample size (639) was large enough for MAIC

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Benralizumab vs reslizumab

- Benralizumab and reslizumab trials varied in sample size, disease severity, medium-dose ICS cut-off, exacerbation history in previous year, and baseline EOS count; (low to moderate overlap in the trial population in terms of exacerbation history within the past year).
  - High heterogeneity across the baseline characteristics in the two studies identified giving an effective sample size of 20 rendering MAIC infeasible
  - Extreme weights for some patients during matching are produced which indicates lack of population overlap and decreases statistical power to detect differences between treatments
  - Differences in inclusion criteria and dosing schedule for OCS sparing trials could not be adjusted for using MAIC
- MAIC analysis was considered unfeasible and equivalent clinical efficacy was assumed for benralizumab and reslizumab based on this.
- ERG- there is no evidence to support this strong assumption

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Benralizumab vs mepolizumab
MAIC exacerbation results

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched): RR (95% CI)	
SIROCCO/ CALIMA vs. MENSA/DREAM	Annualised rate of clinically significant exacerbations	[redacted]	[redacted]
	Annualised exacerbation rate leading to ER/hospitalisation	[redacted]	[redacted]

[redacted]

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Benralizumab vs mepolizumab MAIC OCS sparing results

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched)	
ZONDA vs. SIRIUS	Percentage reduction in OCS dose, mean difference (95% CI)	[redacted]	[redacted]
	Patients with complete reduction in OCS dose, OR (95% CI)	[redacted]	[redacted]
	Annual exacerbation rate reduction/ clinically significant exacerbations, RR (95% CI)	[redacted]	[redacted]

[redacted]

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ERG critique-decision problem and risk of bias in trials

- Company considers SoC to be most relevant comparator.
- ERG's clinical adviser suggests only people who do not need anti-IL5 therapy would receive SoC (~5% of people with severe asthma).
- Most people would receive mepolizumab and only a minority (up to 5%) would receive reslizumab because of its intravenous route of administration
  - ERG considers mepolizumab the most relevant comparator
- ERG had concerns regarding selective reporting of some trial secondary outcomes. No concerns regarding primary outcomes
- There were many unreported secondary outcomes across all 3 main studies that may potentially be relevant
- In ZONDA, baseline blood eosinophil count was imbalanced between treatment arms, therefore groups cannot be considered similar at the outset in terms of prognostic factors

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ERG critique-trial results

- SoC and results in pivotal trials consistent with current UK guidelines/ practice
- Similar proportion of people with ≥ 3 exacerbations in the previous year in CALIMA (39.4%) and SIROCCO (41.4%) Q8W which is expected due to similarly stratified randomisation procedure in the two trials
- Difference in magnitude of treatment effect between the SIROCCO and CALIMA trials is likely to be related to unknown confounders
- Treatment effect of benralizumab appears to consistently favour benralizumab in SIROCCO and CALIMA only for the Asian population
- Pooling subgroups from CALIMA and SIROCCO was appropriate
  - higher exacerbation reduction for patients with baseline AER ≥ 3, and baseline blood eosinophil counts ≥ 300 cells/µL although confidence intervals overlap
- ZONDA population is less severe than SIROCCO/CALIMA – different prognosis?
- Benralizumab was well tolerated with an adequate safety profile in the short term (up to one year) and including people on mOCS

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ERG critique – MAIC methodology (1)

- MAIC analysis largely conducted according to NICE Decision Support Unit (DSU) recommendations. However, the company did not provide individual patient data (IPD) .
  - ERG could not check the clinical analysis or verify whether the assumptions underpinning the analysis were appropriate
- Inappropriate to assume clinical equivalency for benralizumab and reslizumab (based on comparison of baseline characteristics and ITT results)
  - Different mechanism of action and differences in baseline characteristics of trial populations does not support clinical equivalency.
  - ERG agreed that MAIC comparing benralizumab with reslizumab appeared unfeasible
- There was evidence of selective outcome reporting, whereby outcomes in all trials for which benralizumab had unfavourable results in the CSR were not reported by the company or considered as clinical inputs to the economic model.
- The MUSCA trial was not included in the base case MAIC (because the primary outcome was HRQOL and was not powered to detect differences in efficacy). Results including the MUSCA trial were less favourable to benralizumab

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Benralizumab vs mepolizumab
MAIC including MUSCA

- No statistically significant difference with the inclusion of MUSCA, however results favour mepolizumab not benralizumab. This has big impact on the ICERs when the comparator PAS's are used
- Pooled MAIC results for clinically significant exacerbations for MUSCA:

Comparison	RR	LCI	UCI
BENRA Q8W vs placebo, unadjusted (SIROCCO/CALIMA)	[redacted]	[redacted]	[redacted]
MEPO vs placebo, unadjusted (MENSA/DREAM/MUSCA)	[redacted]	[redacted]	[redacted]
BENRA Q8W vs placebo, adjusted for MENSA/DREAM/MUSCA	[redacted]	[redacted]	[redacted]

[redacted]

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ERG critique – MAIC methodology (2)

- The effect modifier selection process for the MAIC analysis excluded clinically significant effect modifiers such as age, race, BMI, FEV1, nicotine status, and atopic status. These were not selected for matching in the MAIC because there was not an imbalance between benralizumab and mepolizumab trials (contrary to NICE DSU recommendations)
  - Approach based on a combination of literature searches, statistical analysis and clinical opinion to identify effect modifiers and prognostic factors
  - ERG noted it was unclear whether open elicitation of potential effect modifiers from clinicians or clinical input on pre-selected variables was sought

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ERG critique – MAIC methodology (3)

- Data were imputed from one technology to another despite benralizumab having a fundamentally different mechanism of action from mepolizumab
  - MAIC analysis comparing benralizumab and mepolizumab conducted in full trial populations as relevant subgroup data not available for competitor trials
  - The ERG considered it unreasonable to assume the relative efficacy between the ITT population and severe sub-group would be equal for benralizumab and mepolizumab. The ERG noted that even though both mepolizumab and reslizumab are more efficacious in the more severe subgroup, they may not be efficacious by the same amount

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