NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Benralizumab for treating severe eosinophilic asthma [ID1129]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Benralizumab for treating severe eosinophilic asthma [ID1129]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing
Benralizumab for treating inadequately controlled asthma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Abbreviations

AER	annual asthma exacerbation rate	NMA	network meta-analysis
BTS	British thoracic society	HRQoL	health-related quality of life
IL	interleukin	Q4W	once every 4 weeks
IHS	inhaled corticosteroids	Q8W	once every 8 weeks
IPD	Individual patient data	SC	sub-cutaneous
ITT	intention to treat	SmPC	Summary of products characteristics
OCS	oral corticosteroid	SoC	standard of care
LABA	long-acting β-agonists	STA	Single technology appraisal
MART	maintenance and reliever therapy		

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Key issues: Clinical effectiveness

- Does benralizumab have any particular advantages over other available treatments and where would it fit in the clinical pathway?
- Which is the most relevant comparator (company proposes SOC but clinical adviser to the ERG cites mepolizumab in 90% of patients)
- What are the most clinically relevant outcomes (annual number and severity of exacerbations, rescue medication, lung function, mOCS use and other secondary outcomes)?
- Is benralizumab clinically effective compared with standard of care?
- Is it reasonable to assume that benralizumab and reslizumab are clinically equivalent given different modes of action?
- Is the MAIC of benralizumab compared with mepolizumab robust? Is there a clinically meaningful difference in the clinical effectiveness of benralizumab and mepolizumab?

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Key issues: Subgroups and comparators

Is the treatment effect likely to differ depending on previous annual exacerbation rate and/or by use of maintenance oral corticosteroids?

What is the committee's view of the evidence for and relevance of the proposed subgroup?

The company modelled the subgroup of patients with 3+ exacerbations in the previous 12 months or on mOCS for the previous 6 months. Does the committee consider the subgroup to be homogeneous, or should it be separated by further subgroups of people not on mOCS and people on mOCS?

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?

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Disease Background

- Asthma is a disease of airways
- Symptoms such as breathlessness, chest tightness, wheezing, cough
- 4.8 million people in England and Wales, in 2015 there were 1,468 asthma related deaths in the UK
- 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

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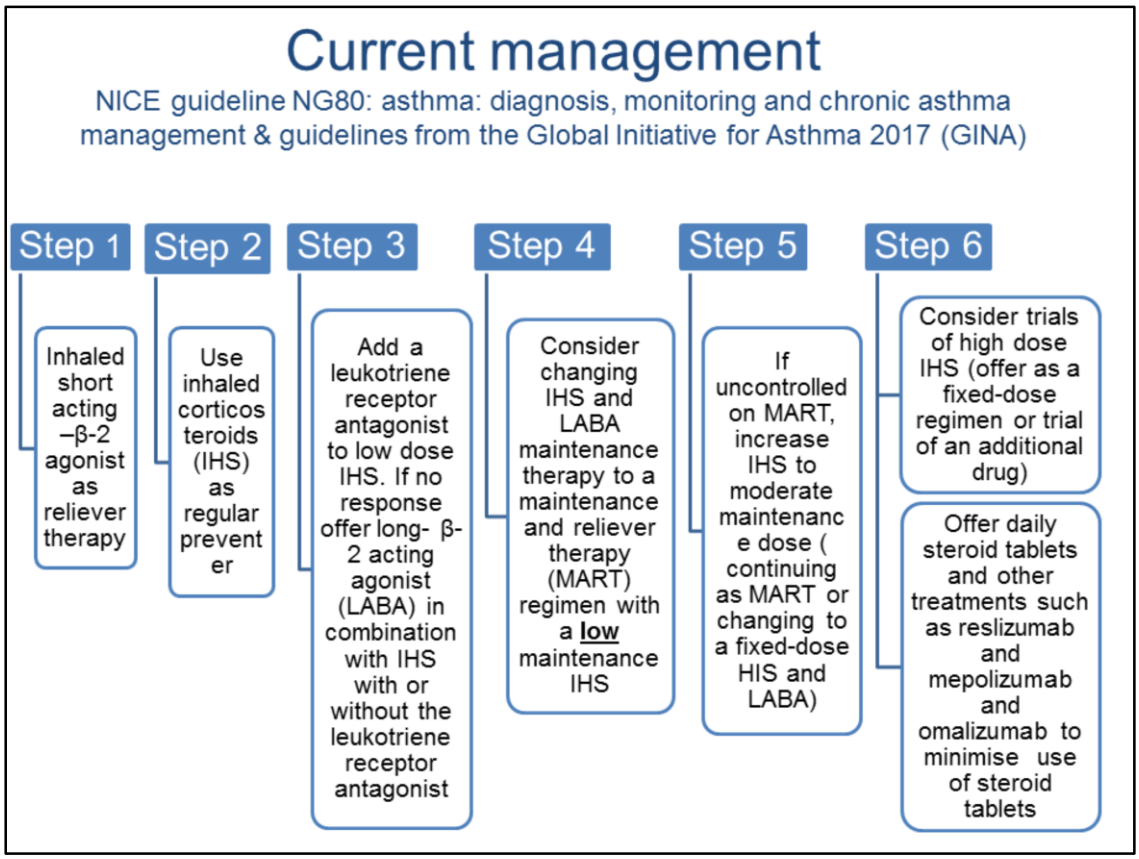
Further detail and discussion on the background can be found in page 39-58 of the company submission

Eosinophilic inflammation is common in asthma with approximately 50% of all patients with asthma having eosinophilic inflammation.

Asthma accounts for high numbers of consultations in primary care, out-of-hours services and hospital emergency departments; during 2011–2, there were over 65,000 hospital admissions for asthma in the UK

In 2015, 1,468 people died due to asthma in the UK, the highest level for over 10 years



Further detail and discussion on the management of severe asthma can be found in pages 42-56 of the company submission

Guidance from the recently published NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and recent guidelines from the Global Initiative for Asthma (GINA) replace management based on a combination of guidance from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN)

New biological treatment options for people with severe asthma Inadequately controlled with medium to high dose ICS in combination with other controller medications have recently been recommended by NICE. Continuing to increase ICS dose or adding OCS are options, but as high-dose and long-term use of corticosteroids are associated with a range of adverse effects, guidelines state that ICS and OCS should be used at the lowest doses at which asthma control is maintained and other treatments should be considered to minimise the use of steroid tablets.

Previous appraisals

Biologics recommended by NICE for treating eosinophilic asthma:

- NICE TA431 **(2017)** recommends mepolizumab for treating severe refractory eosinophilic asthma, in adults with a blood eosinophil count of **300 cells/microlitre** or more in the previous 12 months, and have has 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 for treating severe eosinophilic asthma that is inadequately controlled in adults with a blood eosinophil count has been recorded as **400 cells per microlitre** or more and have had **3 or more** severe asthma exacerbations needing systemic corticosteroids in the past 12 months

Biologics recommended by NICE for treating allergic IgE-mediated asthma:

- 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).

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

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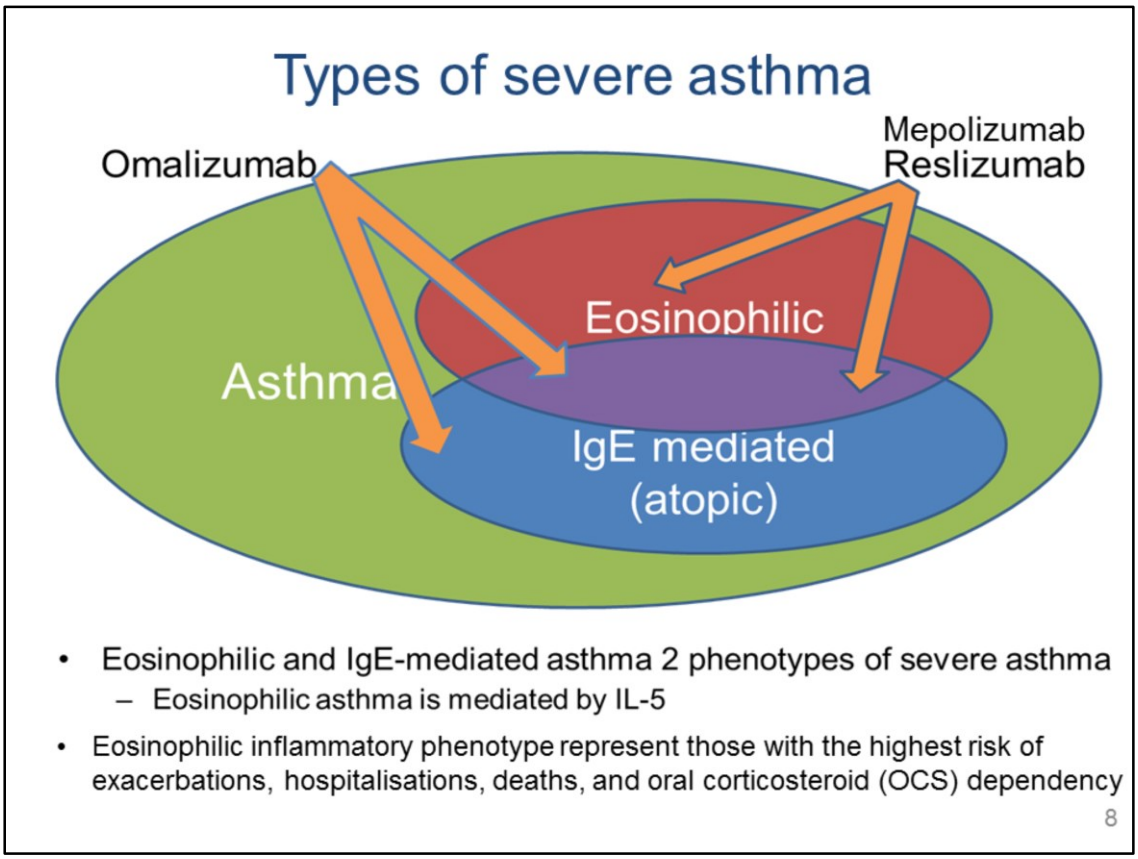

Source: Related reslizumab PMB, slide 3

Eosinophils are a type of white blood cell that play a major role in airway inflammation in asthma are associated with allergic sensitisation and part of the inflammatory response

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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Further detail can be found in the expert submissions documents

Asthma UK – "The introduction of biologics to treat asthma has proved to be life-transforming for people with severe asthma who are eligible for them. For example, Jane Farmilo, who was diagnosed with severe eosinophilic asthma and started taking mepolizumab said "Two weeks after my first injection I could climb hills in the Peak District. After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I'm actually thinking about increasing the number of hours I do. This treatment has really transformed my life."

Expert Comments (BTS/RCP)

- Aim of treatment - reduction in number of clinically important exacerbations, improved lung function and reduction in OCS use in people with severe difficult to control asthma
- Severe asthma is usually treated with either OCS or monoclonal antibodies (omalizumab, mepolizumab or reslizumab) in the NHS
- Benralizumab would allow for additional options besides OCS to become available to patients and would therefore have steroid sparing properties. The reduced incidence of the side effects associated with OCS (such as weight gain, skin thinning, increased risk of infection, osteoporosis, cataracts, gastritis and osteonecrosis) would normally not be incorporated in a quality-adjusted life year (QALY)
- 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
- Benralizumab administered as injection which will have detrimental effects due to pain and inconvenience of visits to a healthcare centre
- 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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Further detail can be found in the expert submissions documents

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 real-world 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]
  - [redacted]

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Further detail and discussion on the burden of OCS use can be found in pages 45-52 of the company submission

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Details of the technology

Technology	Benralizumab (Fasenra, AstraZeneca)
Marketing authorisation	Indicated as an add-on maintenance treatment in adult patients with 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 products that achieve eosinophil reduction through the indirect mechanism of IL-5 neutralisation (mepolizumab, reslizumab), which results in eosinophil reduction, but not depletion.
Administration	30 mg dose once every 4 weeks for first 3 doses, then once every 8 weeks thereafter as sub-cutaneous (SC) injection through an accessorised pre-filled syringe
Acquisition cost	Anticipated list price: £[redacted] (30 mg SC injection) PAS price: £[redacted] (30 mg SC injection) Treatment duration is lifetime

Further detail and discussion on details of the technology can be found in pages 33-38 of the company submission

	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 IHS 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 SOC main comparator **ERG** - mepolizumab more appropriate
Outcomes	• asthma control • incidence of exacerbations • use of oral corticosteroids • evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life	As per scope

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Further detail and discussion on details of the technology can be found in pages 33-38 of the company submission

No notes on this page.

Benralizumab clinical studies (1)

Trial design: All studies phase III, randomised, double-blind and parallel group			
Study	**Population (ITT)**	**Intervention**	**Comparator**
SIROCCO (n=1205)	Patients 12–75 years with uncontrolled asthma receiving **high dose** ICS and LABA, history of **2 or more asthma exacerbations** in prior year, pre-specified blood eosinophil ≥300/µL (N.B. high dose ≥ **800µg** FP daily)	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)	Patients 12–75 years with uncontrolled asthma receiving **medium to high dose*** ICS and LABA, history of **2 or more asthma exacerbations** in prior year, pre-specified blood eosinophil ≥300/µL n=215 (16%) received medium-dose ICS (≥ **500µg** FP daily) plus 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) **	
Zonda (n=206)	Patients aged 18–75 years with uncontrolled asthma receiving **high-dose*** ICS and LABA, history of **1 or more asthma exacerbations** in prior year, with 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

See company submission, table 11 and 12, pages 66-69 and pages 70-74 for more information

*Medium dose defined as >250µg FP equivalent per day and high dose as >500µg for adults

NOTE: The trials include people with **1 or 2 more exacerbation**s per month and defined high dose ICS as
>500µg for adults whereas a NICE recommendation is sought for the subgroup of adults with severe eosinophilic asthma that is inadequately controlled, despite high-dose inhaled corticosteroids (ICS) (≥ **800µg** FP daily) and **3 or more** asthma exacerbations needing systemic corticosteroids in the previous 12 months

The 8 Wk dosing regimen was for adults and non-EU adolescents. The rationale for different dosing regimen in adolescents in the EU was based on the Paediatric Committee at the European Medicines Agency's (PDCO) request to limit drug burden in adolescents and to study only the less frequent dose in this patient population

For EU adolescents, the dosing regimens were:

SIROCCO: 30 mg subcutaneous injection for 48 weeks treatment period of benralizumab Q4W x 3 and Q8W x 4

CALIMA: 30 mg subcutaneous injection for 56 weeks treatment period of benralizumab

Q4W x 3 and Q8W x 5

ZONDA did not include adolescents

*Medium dose defined as >250µg FP equivalent per day and high dose as >500µg for adults

Benralizumab clinical studies (2)

Study	Outcomes	Pre-defined subgroups	Settings
SIROCCO (n=1204)	**Primary outcome:** Annual asthma exacerbation rate (AER) ratio versus placebo* **Secondary outcomes:** • pre-bronchodilator forced expiratory volume in 1 second (FEV1) • Total asthma symptom score - week 48 • health related quality of life (HRQoL) • healthcare resource use utilisation • adverse events	• Baseline OCS use (yes/no) • Sex (male/female) • Age (<18, 18–<65, or ≥65 yrs) • Geographic region (Asia, Eastern Europe, Europe [excluding Eastern Europe], North America, South America • Body mass index (≤35/>35 kg/m2) • Number of exacerbations in previous year (2, 3, or ≥4). • Race (white, black or African-American, Asian, or other). • Nasal polyps at baseline (yes/no) • Immunoglobulin E at baseline (≤30, >30–≤700, or >700 IU/L) • Atopic asthma at baseline (yes/no) • Prior treatment with omalizumab (yes/no)	374 centres in 17 countries, including 24 UK centres
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		303 centres in 11 countries
Zonda (n=220)	**Primary outcome:** Percentage reduction in oral glucocorticoid dose from baseline 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	89 centres in 12 countries

See company submission, table 11 and 12, pages 66-69 and pages 75-76 for more information

An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) emergency department or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥24 h) because of asthma.

AER summarised as total number of exacerbations x 365.25/total duration of follow-up within the treatment group (days). An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) emergency department or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥24 h) because of asthma

The total asthma symptom score is a composite of morning assessments of asthma symptoms, night-time awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater

symptom burden.

Primary and key secondary analyses of efficacy included people with blood eosinophil counts at least 300 cells per µL. (All efficacy endpoints were also assessed in patients with blood eosinophil counts less than 300 cells per µL, but statistical comparisons were not done for patients with less than 300 eosinophils per µL for non-key secondary outcomes (except for ACQ-6)

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; p value)	-	0.49 (0.37–0.64; <0.0001)
Key secondary endpoints (48 weeks)		
Pre-bronchodilator FEV_1		
Number of patients	261	264
Least square (LS) mean change (number of patients)	0.239 (233)	0.398 (235)
LS mean difference *vs* placebo (95% CI; p value)	-	0.159 (0.068 - 0.249; 0.0006)
Total asthma symptom score (decrease in score represents improvement)		
Number of patients analysed^	267	263
LS mean change (number of patients)	−1.04 (180)	−1.30 (178)
LS mean difference *vs* placebo (95% CI; p value)	-	−0.25 (−0.45 - −0.06; 0.0118)
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; p value)	[redacted]	[redacted]

title corrected to reflect ITT results
^ People with a baseline and at least one post-baseline assessment. ^^excludes adolescents

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Source: Table 19 (page 97 of the company submission) . Also see company submission pages 76-78 and 96-98 for more information

*Company submission reports results for patient subgroup for which a NICE recommendation is sought (i.e., patients with, or ≥6 months previous treatment with OCS)

AER, FEV 1 and total asthmas score estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations

*** Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment

Baseline characteristics were similar between treatment arms, as well as between patients with blood eosinophil counts at least 300 cells per µL and less than 300 cells per µL . Use of maintenance asthma treatment use was similar across groups, with a mean fluticasone propionate or equivalent total daily dosage of 899 µg (range 125–3000). Overall, 196 (16%) patients were receiving oral corticosteroids, with similar dosing between cohorts

Clinical effectiveness ITT results: 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; p value)	-	0.72 (0.54–0.95; 0.0188)
Key secondary endpoints (48 weeks)		
Prebronchodilator FEV_1 (L)		
Number of patients	244	238
LS mean change (number of patients)	0.215; 221	0.330; 211
LS mean difference *vs* placebo (95% CI; p value)	-	0.116 (0.028–0.204; 0.0102)
Total asthma symptom score (a decrease in score indicates improvement)		
Number of patients analysed^	247	237
LS mean change (number of patients); patients at 56 weeks	−1.16; 187	−1.40; 185
LS mean difference *vs* placebo (95% CI; p value)	-	−0.23 (−0.43 to −0.04; 0.0186)
EQ-5D- 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; p value)	[redacted]	[redacted]

*title corrected to reflect ITT results
^ People with a baseline and at least one post-baseline assessment.
^^excludes adolescents

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Source: Table 20 (page 98-99 of the company submission) . Also see company submission pages 98-99 for more information
Patient demographics and baseline clinical characteristics were balanced across treatment groups and by eosinophil count (at least 300 cells per µL versus less than 300 cells per µL)

AER and total asthma score estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations

FEV1 estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.

Heterogeneity in regional exacerbation rates between SIROCCO and CALIMA despite similar trial design

- 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 resulting reduction in exacerbation rates with benralizumab were numerically greater.
- Subgroup of people 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%) Q8W.

  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 do not agree – difference 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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Please see pages 99-101 of the company submission for more information

Analyses of exacerbation rates by region were explanatory and not powered to detect difference (small n numbers in each group).

Pooled clinical effectiveness results: SIROCCO and CALIMA

- A pre-specified pooled efficacy analysis was conducted (similar trial designs) to better understand the relationship between baseline blood eosinophils and effectiveness of benralizumab
- 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 demonstrates that exacerbation reduction was dependant 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 BUT there is uncertainty associated with results as confidence intervals overlap

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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

* slide included before the committee meeting

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Clinical effectiveness results: ZONDA

Note: 1 or more asthma exacerbations in prior year, with blood eosinophils ≥150/µL

	Placebo (N=75)	Benralizumab Q8W (N=73)
Primary outcome: median OCS dose (range) – mg/day		
At baseline	10.0 (7.5 – 40.0)	10.0 (7.5 – 40.0)
At final visit	10.0 (0.0 – 40.0)	5.0 (0.0 – 30.0)
Median reduction from baseline(range)	25.0 (-150 – 100)	75.0 (-50 – 100)
Reduction from baseline in final OCS dose, n (%)		
≥90%	9 (12)	27 (37)
≥70%	15 (20)	37 (51)
≥50%	28 (37)	48 (66)
>0%	40 (53)	58 (79)
Any increase or no change in dose	35 (47)	15 (21)
Analysis of % reduction from baseline in OCS dose		
Odds ratio (95% CI; p value)	-	4.12 (2.22 – 7.63; p<0.001)
Key secondary outcomes		
Annual asthma exacerbation rate	1.83	0.54
Rate ratio (95% CI; p value)	-	0.30 (0.17 to 0.53; p<0.001)
Pre-bronchodilator FEV1	0.126	0.239
LS mean difference	-	0.112 (95% CI, –0.033 to 0.258; p=0.129)

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Source: Table 21(page 105 of company submission). Also see company submission pages 103-105 for more information

A total of 220 patients underwent randomisation and received study treatment in the ZONDA trial. Baseline characteristics were balanced between arms, with the exception of the median baseline blood eosinophil count, which was lower in the benralizumab 30 mg Q4W and Q8W groups compared with the placebo group

The baseline OCS dose was the daily dose at which the patient's asthma was stabilised at randomisation and the final OCS dose was the final daily dose at week 28

Subgroup analysis of ZONDA
Adult patients with 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)	[redacted]	[redacted]
Comparison (difference between medians); P value	[redacted]	
Eligible patients with 100% reduction from baseline in final OCS dose	[redacted]	[redacted]
Comparison (difference between medians); P value	[redacted]	
Annual exacerbation rate ; P value	[redacted]	[redacted]
Comparison (rate ratio)	[redacted]	
FEV1 pre-bronchodilator change from baseline (L)	[redacted]	[redacted]
Comparison (difference in LS means); P value	[redacted]	
Total asthma symptom score change from baseline	[redacted]	[redacted]
Comparison (difference in LS means); P value	[redacted]	

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Source: Table 25(page 110 of company submission). Also see company submission pages 108-110 for more information

Adverse events (AEs)

- Benralizumab is well tolerated, with rates of AEs, serious AEs, and AEs leading to discontinuation of treatment similar between benralizumab and placebo
- Most AEs observed were mild to moderate in intensity and not related to treatment
- Common AEs across trials included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis
- **ITT:** Adverse events leading to treatment discontinuation were slightly more frequent in the benralizumab Q8W and Q4W groups (2%) than in the placebo groups (<1%) in both the SIROCCO and CALIMA studies.
- In the **pooled SIROCCO and CALIMA subgroup analysis** (for patients inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl AND ≥3 prior asthma exacerbations), 80.5% of people recieving benralizumab experienced an AE compared with 81.6% receiving placebo. Rate of AEs leading to discontinuation of treatment was 4.1% versus 0.7%. One patient in the benralizumab arm died due to an AE not considered to be drug related
- [redacted]

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Further detail and discussion on adverse events can be found in pages126-130 of the company submission

In the pooled SIROCCO and CALIMA subgroup analysis (for patients inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl AND ≥3 prior asthma exacerbations), the rate of serious AEs was 17.9% in the benralizumab group and 11.8% in the placebo group, while the rate of AEs leading to discontinuation of treatment was 4.1% versus 0.7%, respectively.

[redacted]

Approach to comparison with existing biologics
Matching adjusted indirect comparison (MAIC) – ITT

- Network meta-analysis (NMA) ruled out by company due to significant differences between benralizumab, mepolizumab and reslizumab trials
- Anchored MAIC approach chosen to adjust for the cross-trial differences in patient characteristics to produce less biased estimates of effects when compared with standard indirect treatment comparison
- Literature identified effect modifiers validated by external clinical experts:
  - Exacerbation trials - AER, AER requiring the A&E admissions or hospitalisation, pre-bronchodilator FEV1,
  - OCS sparing trials - percentage reduction from baseline OCS dose and proportion of patients with 100% reduction in OCS dose
- The selection of studies and patient population considered for inclusion in the MAIC for comparison of reslizumab and mepolizumab against benralizumab included:
  - only Phase III pivotal trials evaluating approved respiratory biologics in severe uncontrolled asthma on **high-dose** ICS plus at least one additional controller
  - Only subgroup receiving high-dose ICS from CALIMA included
  - Studies evaluating only EMA licensed or US FDA licensed doses of respiratory biologics
- **However 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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Please refer to Appendix D for detailed methodology of the MAIC and pages 110-118 as well pages 124-125 of the company submission for further information on the reasoning for the MAIC approach

Identification of treatment effect modifiers -section D.1.2, page 361-365 and page 383-387 for more information on the selection of effect modifiers and prognostic variables

An anchored MAIC method was adopted based on the following rationale:

- Benralizumab and other in-scope biologics (mepolizumab and reslizumab) share a common control group (placebo)
- MAIC is preferred to simulated treatment comparison as it avoids the need to assume a relationship between the effect outcome,(e.g., exacerbation rates), and the ‘matching’ characteristic

Matching adjusted indirect comparison (MAIC) 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
- Therefore, 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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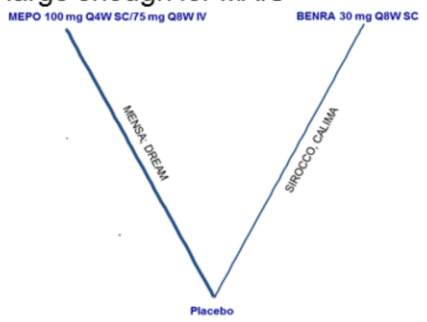
Please refer to Appendix D for detailed methodology of the MAIC and pages 110-118 as well pages 124-125 of the company submission for further information on the reasoning for the MAIC approach

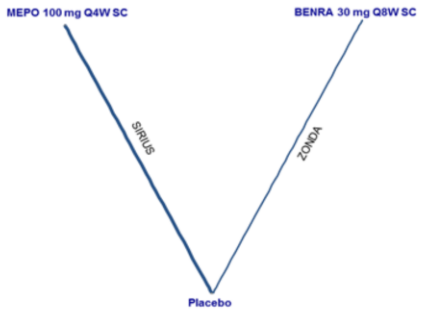
*The benralizumab and reslizumab trials varied in terms of sample size, disease severity, medium-dose ICS cut-off, exacerbation history in previous year, and baseline EOS count; there was very low to moderate overlap in the benralizumab and reslizumab trial population in terms of exacerbation history within the past year

Matching adjusted indirect comparison (MAIC) Benralizumab vs mepolizumab - exacerbations

- 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



(a) Exacerbation trials



(a) OCS sparing trials

27

Source: Figure 22 (page 120 of the company submission). Further detail and discussion on details of the evidence network for comparison of benralizumab versus mepolizumab for annual rate of clinically significant exacerbations, annual rate of exacerbations leading to ER visit/hospitalisation and change from baseline in pre-bronchodilator FEV1 can be found in pages 119-120 of the company submission

Benralizumab vs mepolizumab
MAIC exacerbation results

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched): RR (95% CI)	
SIROCCO/ CALIMA vs. MENSA/DR EAM	Annualised rate of clinically significant exacerbations	[redacted]	[redacted]
	FEV1 at week 32	[redacted]	[redacted]
	Annualised exacerbation rate leading to ER/hospitalisation	[redacted]	[redacted]

Base case MAIC results for clinically significant exacerbations (≥ 880 µg FP daily)

Base case MAIC results for change from baseline in pre-bronchodilator FEV1 (L) (≥ 880 µg FP daily)

28

Source: Table 29 , figure 23 and figure 25 (pages 121-122 of the company submission). Also, please refer to Appendix D for detailed methodology of the MAIC and pages 120-122 of the company submission

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]

Base case MAIC results for percent reduction in OCS dose at 24 weeks

Base case MAIC results for annual rate of clinically significant exacerbations

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Source: Table 30 , figure 26 and figure 28 (pages 122-123 of the company submission). Also, please refer to Appendix D for detailed methodology of the MAIC and pages 122-123 of the company submission

Small ESS can indicate that some patients are receiving extreme weights, and there may be little statistical power to detect differences between treatments. This situation was seen in the sensitivity analysis for the OCS sparing trials (ZONDA vs SIRIUS, with matching for two additional variables, i.e., the proportion of patients with a history of omalizumab use and ACQ-5 scores), wherein the ESS reduced to 44 after matching due to a skewed distribution of weights. As such, results of this sensitivity analysis should be interpreted with caution.

Across the OCS sparing trials, the studies varied in terms of the eligibility criteria for OCS discontinuation, and the dosing schedule for reduction of OCS. These differences could not be adjusted for using MAIC, so the results of the OCS-sparing trials analyses should be interpreted with caution.

ERG critique-decision problem and risk of bias in trials

- Company considers SoC to be most relevant comparator for benralizumab.
- 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

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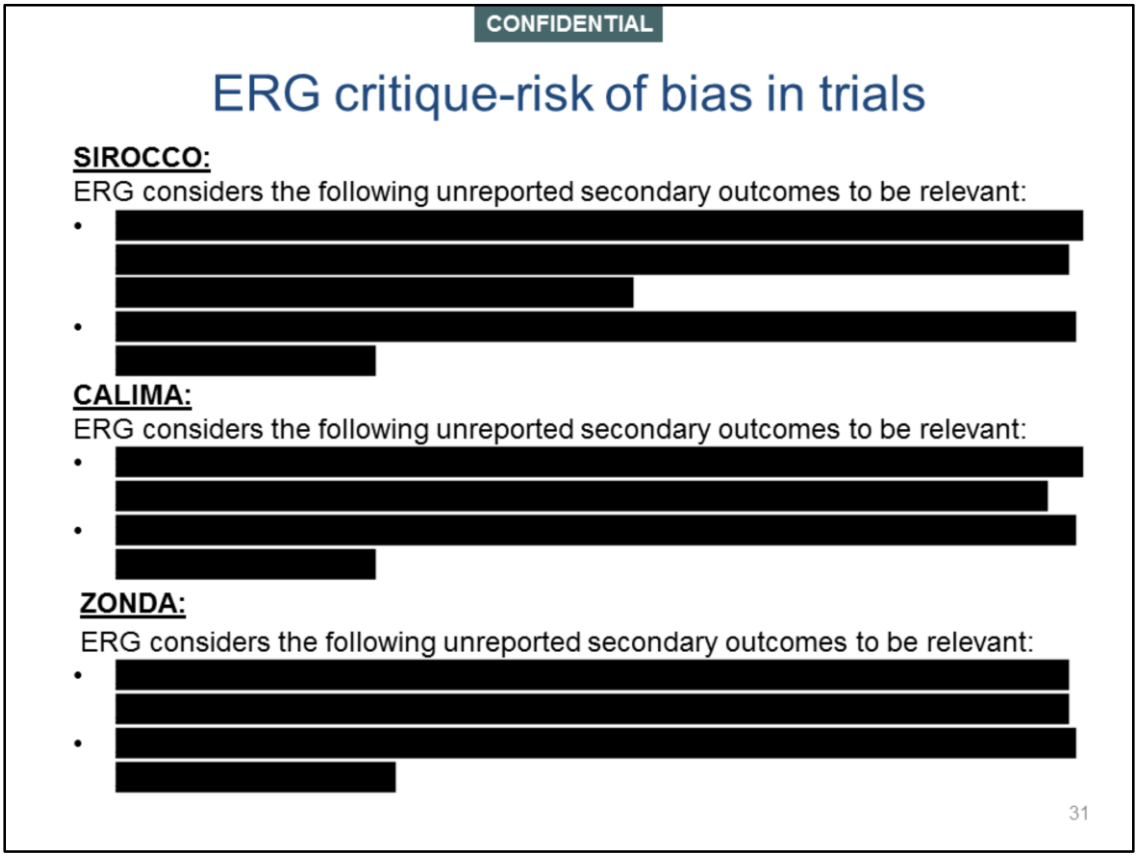
Please see page 42 and pages 53- 55 of the ERG report for more information



Please see pages 55- 59 of the ERG report for more information

ERG critique-trial results 1

- SoC and results in pivotal trials consistent with current UK guidelines/ practice
- Similar proportion with ≥ 3 exacerbations in the previous year in CALIMA (39.4%) and SIROCCO (41.4%) Q8W as expected due to similarly stratified randomisation
- Differences in AER (higher in SIROCCO than in CALIMA) were **NOT due to**
  - regional differences and fewer Eastern Europe/South American patients (similar proportion in SIROCCO [41.4%] CALIMA [39.4%])
  - placebo response in CALIMA (similar AER in previous year CALIMA (1.87) and SIROCCO (1.77)
- Difference in magnitude of treatment effect in both trials is more likely to be related to unknown confounders
- ERG note that the 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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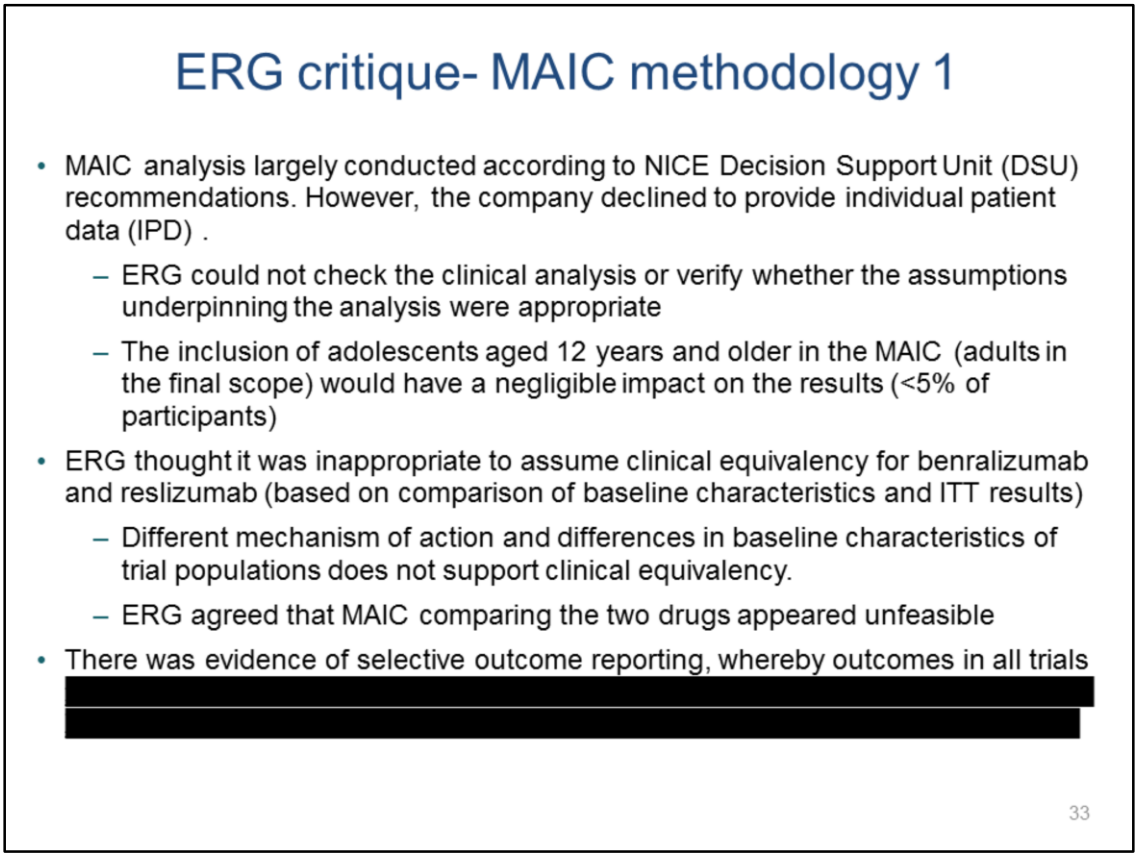
Please see pages 78- 80 of the ERG report for more information



Please see page 98- 106 of the ERG report for more information on the MAIC comparison between benralizumab and reslizumab

Please see page 106- 113 of the ERG report for more information on the MAIC comparison between benralizumab and mepolizumab

ERG critique- MAIC methodology 2

- The effect modifier selection process for the MAIC analysis excluded statistically 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 a significant 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
- Data were imputed from one technology to another despite benralizumab having a fundamentally different mechanism of action from mepolizumab and reslizumab
  - MAIC analysis comparing benralizumab and mepolizumab conducted in full trial populations as relevant subgroup data not available for competitor trials
  - MAIC was conducted in the ITT population. 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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Please see page 98- 106 of the ERG report for more information on the MAIC comparison between benralizumab and reslizumab

Please see page 106- 113 of the ERG report for more information on the MAIC comparison between benralizumab and mepolizumab

No notes on this page.

Key issues: Cost effectiveness (1)

- What is the committee's view about the estimates of asthma-related mortality risk used in the model?
- The company uses the relative treatment effect from the MAIC on the full MENSA/DREAM trials and generalises it to the subgroup with 4+ exacerbations. What is the committee view on whether it is appropriate to assume the same relative treatment effect irrespective of prior number of exacerbations?

  What is the committee's view on the MAIC including the MUSCA trial?
- The company model assumes that benralizumab has the same clinical effectiveness as reslizumab. Does the committee consider the assumption of clinical equiavalency between reslizumab and benralizumab appropriate?

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Key issues: Cost effectiveness (2)

- Different assumptions to calculate the costs of mepolizumab and reslizumab were made by the company and ERG. Which approach does the committee consider appropriate?
- What is the committee's view of the company's base case ICER against SoC of £34,284 per QALY gained?
- What is the committee's view of the ERG's base case ICER against SoC of £39,135 per QALY gained?
- The comparison of benralizumab with mepolizumab and reslizumab is highly dependent on the assumptions about relative effectiveness and on confidential prices for the biologics. Does the committee accept that benralizumab is cost effective compared to mepolizumab and reslizumab?
- What are the most plausible ICER's?
- Is the technology innovative?

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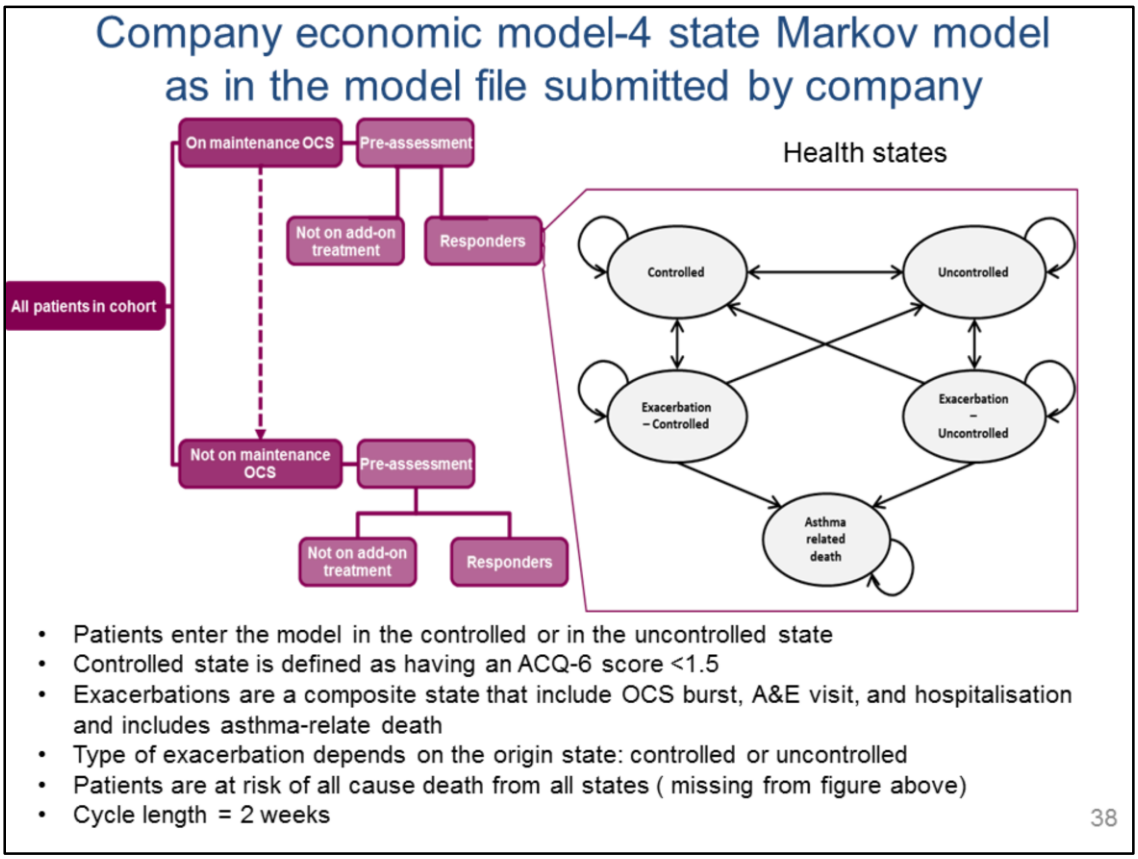
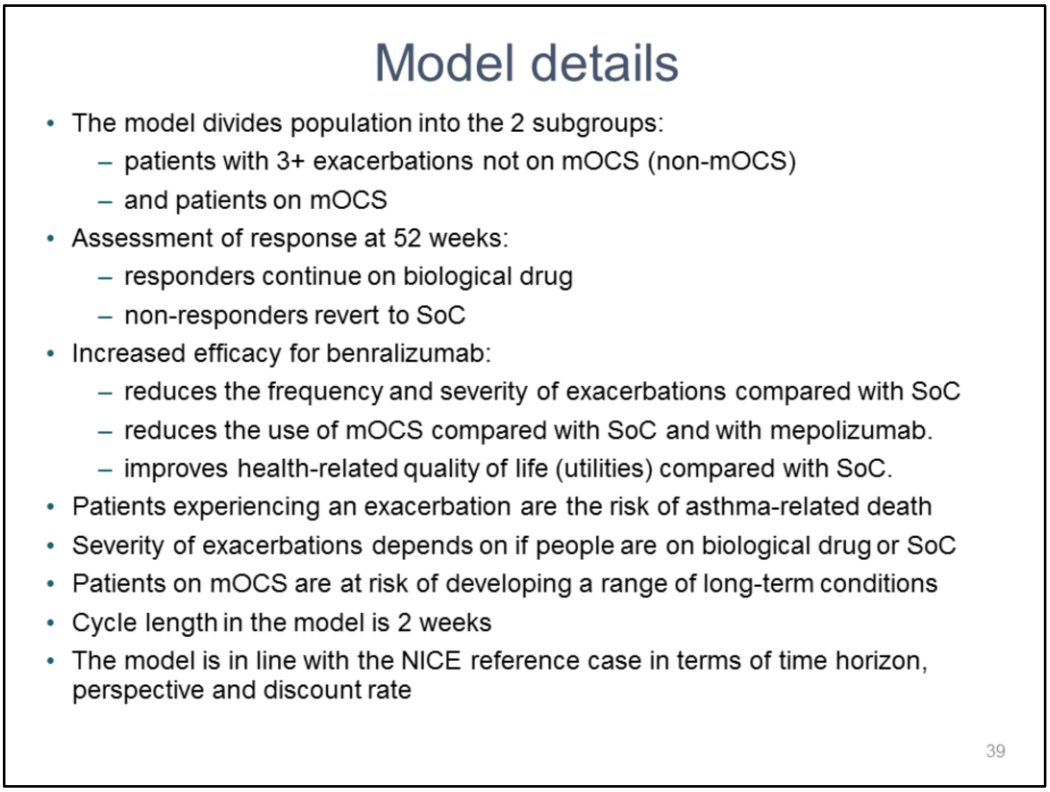


Source: Figure 21, page 143 of the ERG report

Note: The ERG noted that the model structure depicted in the model file differs from the model structure reported in the company submission. The actual model more closely corresponds to the figure shown, though is missing the fact that each exacerbation state is comprised of three different types, and is missing the all-cause mortality state



Please see pages 155-164 ,181 of the company submission, page 20 of the company submission summary and pages 142-153 of the ERG report for more information

After leaving an exacerbation state, patients can return to a controlled or uncontrolled state

Health states in the model are defined as below:

- Controlled Asthma: ACQ-6 score <1.5 (as with precedent from the reslizumab NICE STA)
- Uncontrolled Asthma: ACQ-6 score ≥1.5
- Exacerbations:
    - OCS burst only: Use of systemic corticosteroids (or a temporary increase in a stable mOCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids, with no hospitalisation.
    - Emergency Visit: An urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as above) with no hospitalisation.
    - Hospital admission: An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24

hours) due to asthma.

Assessment of treatment response at 52 weeks defined as a reduction in the number of exacerbations or a reduction in continual use of mOCS after 52 weeks of treatment

Company model
Baseline characteristics

Characteristic	Value	Source
Benralizumab vs. SoC (base case)		
Age (years)	50.2	Pooled SIROCCO/CALIMA
% female	64.5	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	54.1	Kerkhof 2017
Benralizumab vs. Mepolizumab		
Age (years)	49.8	Pooled SIROCCO/CALIMA
% female	66.1	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	78.6	Kerkhof 2017
Benralizumab vs. Reslizumab		
Age (years)	50.2	Pooled SIROCCO/CALIMA
Weight (kg)	75.2	Pooled reslizumab trials
% female	63.3	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	0	NICE Reslizumab STA

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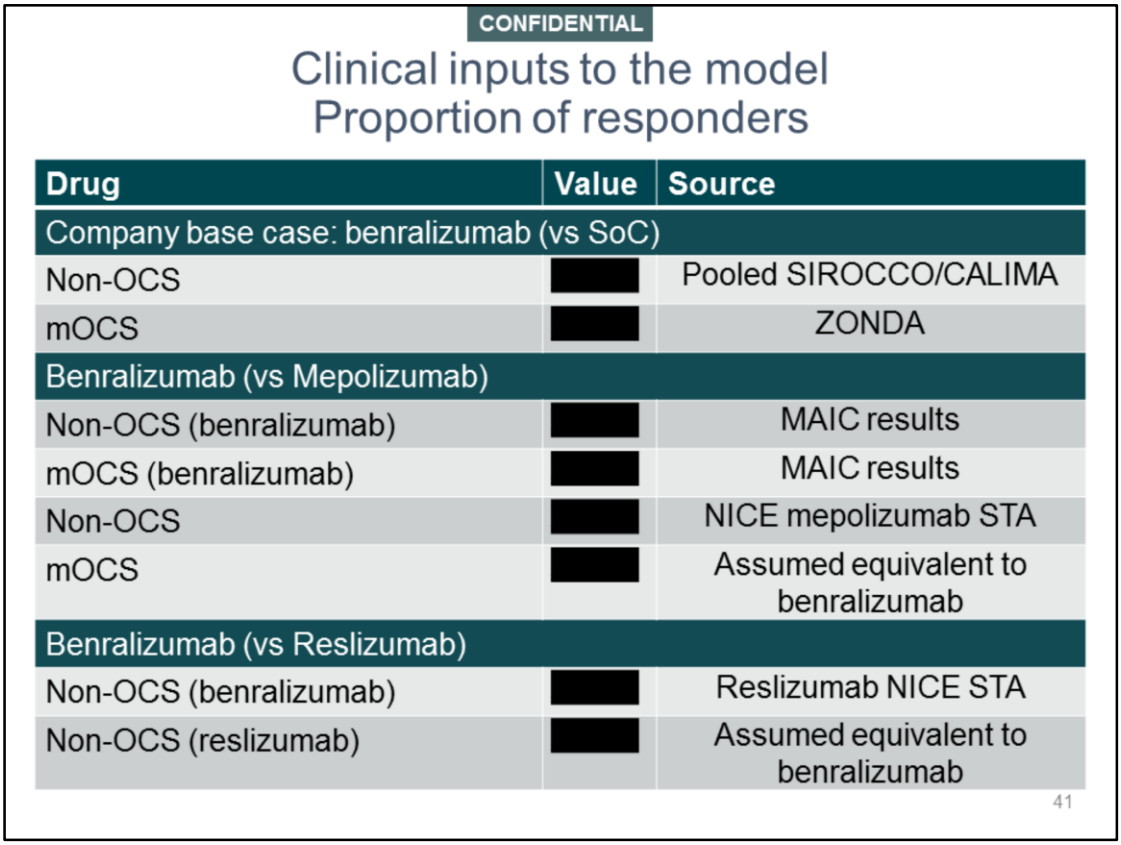
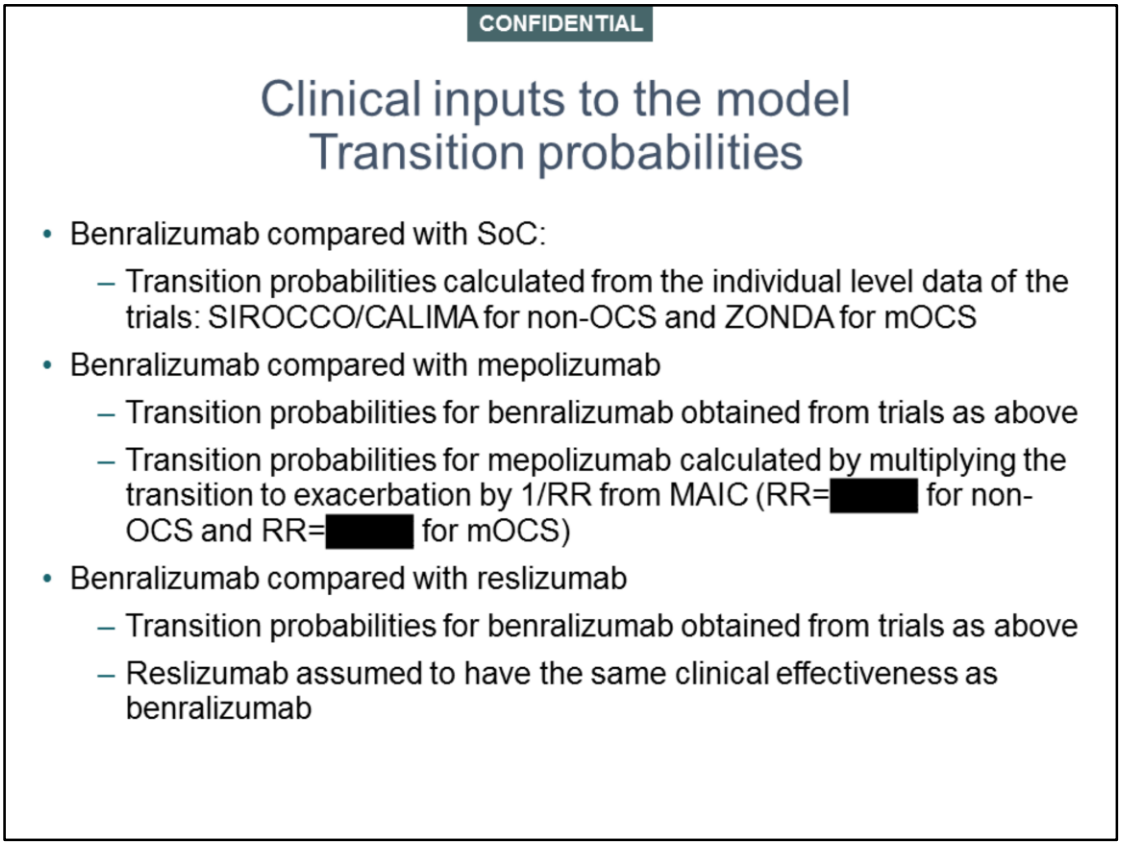
Please see pages 162-164, 167-171 of the company submission and pages 142-153 , table 54 (page 150)of the ERG report for more information

NOTE: The company noted in their company submission that 78.6% of patients on mOCS at baseline was sourced from Kerkhof. However, Kerkhof reported mOCS use in 16.5% in patients 18-64 y.o. (n=313) and 17.1% in patients >=65 y.o. (n=168)
Based on data from a UK registry of patients with difficult to control asthma (Heaney et al., 2010), 41.7% of people are on mOCS. Kerkhof et al. (2017) also reported mOCS use in ~17% of UK patients with severe uncontrolled eosinophilic asthma with *eosinophil count of >=300 cells per µL*. The ERG note the modelled proportions of patients taking mOCS at baseline were not representative of clinical practice in the UK.



Please see pages 170-180 of the company submission for more information

NOTE: The company assume equivalent clinical effectiveness for benralizumab and reslizumab and that the relative effectiveness between the total and subgroup populations are equivalent for benralizumab and mepolizumab. ***This is not the same as equal effectiveness when comparing benralizumab with mepolizumab.*** However equal effectiveness for this comparison has been assumed for treatment response.



Please see pages 165-181 of the company submission and pages 154-156 of the ERG report for more information

Clinical inputs to the model
Reduction in severity of exacerbations

	Non-OCS		mOCS	
	Benralizumab	SoC	Benralizumab	SoC
Exacerbations from controlled state				
OCS burst	16 (100%)	25 (89.29%)	3 (100%)	21 (100%)
A&E	0	1 (3.57%)	0	0
Hospitalisation	0	2 (7.14%)	0	0
Exacerbations from uncontrolled state				
OCS burst	22(81.48%)	99(85.34%)	13(100%)	31(68.89%)
A&E	0	9(7.75%)	0	5 (11.11%)
Hospitalisation	5(18.52%)	8(6.91%)	0	9(20%)

Note: for comparisons with other biologics, the same split as benralizumab is used

See pages 180-181 of the company submission and pages 156-161 of the ERG report for more information

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Clinical inputs to the model
Reduction in mOCS use

Parameter	Value	Source
mOCS use at baseline	[redacted]	ZONDA
Reduction in mOCS use		
Benralizumab	[redacted]	ZONDA
SoC	[redacted]	ZONDA
Mepolizumab	[redacted]	MAIC

In the model, the use of mOCS is associated with increased incidence of long-term conditions: Type 2 diabetes mellitus, osteoporosis, glaucoma, cataracts, myocardial infarction, heart Failure, cerebrovascular accident, renal impairment, peptic ulcer, and pneumonia.

The long-term conditions are associated with costs and disutilities in the long-term

Please see pages 182-183 of the company submission for more information. Data in table is from the model excel file.

Clinical inputs to the model

Other clinical effectiveness parameters and assumptions

1. Benralizumab discontinuation rate is 11.8% (pooled SIROCCO/CALIMA), and assumed the same for mepolizumab
2. 100% adherence to biological drugs.
3. Constant exacerbation rates over time
4. Treatment response sustained over time
5. The impact of adverse drug reactions is negligible

See pages 279-280 of the company submission and Table 100 for more information

Company model
Asthma related mortality

Parameter	Value
During OCS burst	
Age 17-44	0.05%
Age 45+	0.32%
During A&E visit	
Age 17-44	0.32%
Age 45+	2.05%
During hospital admission	
Age 18-24	0.15%
Age 25-34	0.14%
Age 35-44	0.20%
Age 45-54	0.76%
Age 55-64	2.14%
Age 65+	4.54%

- Patients experiencing exacerbations are at risk of asthma-related death
- Exacerbations assumed to last 8 weeks
- Risk of death depends on age and type of exacerbation
- Risk of death obtained from Watson et al, Roberts et al, and NRAD report

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Please see pages 184-191 of the company submission and page 162-167 of the ERG report for more information

Company model
Health state utilities

- EQ-5D-5L data collected during SIROCCO and CALIMA trials and mapped to derive EQ-5D-3L utilities for the health states of the non-OCS subgroup
- AQLQ-12 collected in ZONDA and used to derive EQ-5D-3L utilities for the health states of the mOCS subgroup.
- Utilities vary by:
  - Subgroup: mOCS vs non-OCS
  - Health state: Controlled, uncontrolled, exacerbation with OCS burst, exacerbation with A&E visit, exacerbation with hospitalisaiton.
  - Treatment: Benralizumab compared with SoC (only for health states controlled and uncontrolled)
- Disutility of exacerbations lasts 8 weeks based on Golam et al. (2017). **ERG note that this is much longer than considered in previous appraisals of mepolizumab and reslizumab**

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See pages 191-193 of the company submission and pages 167-171 of the ERG report for more information

Company model
Resource use and costs

Drug costs

- Estimated average cost of SoC sourced from trials defining high dose ICS/LABA using BNF 2017 prices
- Unit cost of benralizumab reflects the cost per 8 weeks. Divided by 4 to adjust to the 2-weekly cycle length. People assumed to receive 8 doses in the first year and 6.5 doses thereafter
- Unit cost of mepolizumab reflects the cost per 4-weeks (administered once every four weeks for all patients, the cost is adjusted to the 2-week cycle length
- Cost of reslizumab based on average patient weight published in the reslizumab NICE appraisal (75.2kg) per 4 weeks and adjusted to 2 week cycle length

Administration costs:

- NICE appraisals for reslizumab and mepolizumab
- SoC associated with no additional drug costs

Health state unit costs

- Unit costs applied to levels of healthcare resource use estimated by WIlson et al. (2014, 2016)

AE costs:

- AEs not included in the model because of small proportions and minor differences between treatment groups (similar incidence of AEs for the placebo group (77.6%) compared with the benralizumab (74.7%) group)

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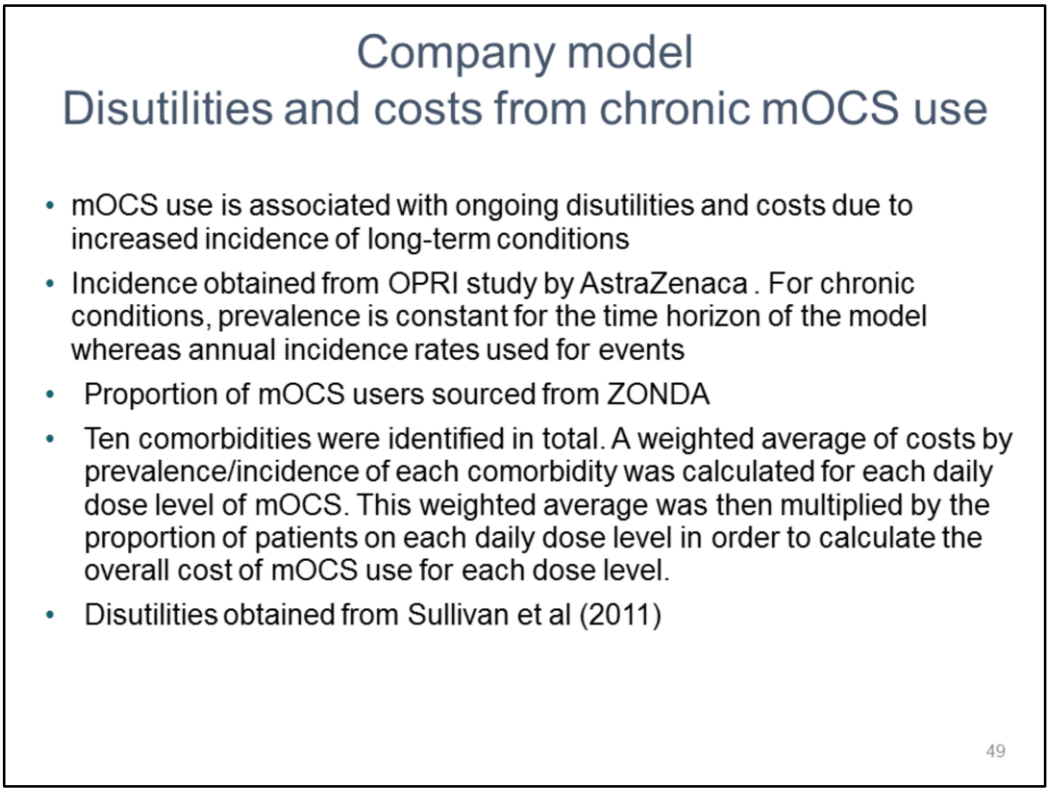
Please see pages 249-258 of the company submission and table 71 (page 183) and table 97 (page 257) for more information

NOTE: In the Willson study, the cycle length of the model was 1-2 week, To align health state costs with the benralizumab model assumption of an exacerbation lasting 8 weeks and is assigned during 4 different cycles, the cost of an exacerbation is divided by 4 to avoid overestimating the cost of exacerbations



Please see page s 249-258 of the company submission and table 71 (page 183) and table 97 (page 257) for more information

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Company model

Base case results (deterministic)

Comparator technology	Population	Inc Costs	Inc QALYs	ICER per QALY
Add-on Benralizumab vs. SOC	Base case	[redacted]	[redacted]	£34,284
Add-on benralizumab vs. Add-on mepolizumab	NICE recommended for mepolizumab	[redacted]	[redacted]	Dominant
Add-on benralizumab vs. Add-on reslizumab	NICE recommended for reslizumab	[redacted]	[redacted]	Dominant

Note: Probabilistic results give similar ICERs

ICERs are based on the benralizumab PAS price and mepolizumab and reslizumab list prices. See confidential part 2 appendix for comparisons with PAS prices

Scenario analyses showed that the results are most sensitive to including risk of asthma death from an exacerbation, equal utility /disutility across treatment arms, costs and utilities associated with mOCS

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Company model: Results of key sensitivity analysis

Sensitivity analysis	ICER vs SoC
Base-case	£34,284
Age at treatment initiation(50.2 years)	£41,807
Utilities independent of treatment	£38,688
Asthma mortality risk =0	£67,260
Removing the consequences of mOCS use	£36,983-£38,573

Sensitivity analyses in comparisons with mepolizumab and reslizumab had negligible impact on the ICER except:
- mepolizumab: proportion of responders on mOCS

In addition:
- PSA
- Threshold analysis on PAS price

See pages 285-298 of the company submission for more information

In order to understand the importance of each parameter in the model and the parameters' individual impact on the cost, effectiveness and cost effectiveness results, a series of deterministic sensitivity analyses were undertaken. Each parameter was set to either the upper and lower limits of the 95% CI, 20% higher or lower than the base case value (where a 95% CI was not available) or standard upper and lower limits holding all other parameters constant.

ERG comments-model structure

- The model structure was appropriate for the economic evaluation
- Model assumed that patients not on mOCS in any given state were be subject to the transition probabilities, costs, and utilities associated with having received mOCS treatment if they were in the mOCS group at baseline
- The model in the reslizumab appraisal included moderate and severe exacerbation states (patients could transition from any asthma state to any exacerbation state) whereas, there was only one exacerbation state from each origin (controlled and uncontrolled) it the benralizumab model. This meant it was not possible to transition between different severities of exacerbation
- 8 weeks exacerbations in the company model based on visual inspection of pooled SIROCCO/CALIMA utility data (time to return to pre-exacerbation utility).
  - the visual inspection method is unclear. Clarification - no systematic method had been used, estimated duration of exacerbation may vary
- NICE **mepolizumab appraisal** - MENSA trial duration of utility decrement was **13 days for OCS burst, 10 days for ED visit, and 21 days for hospitalisation.**
  - duration of disutility applied for each type of exacerbation was substantially overestimated. The shorter durations would be more plausible

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Please see pages 29, 142-145 of the ERG report for more information

ERG comments-clinical inputs to model

- Response criteria consistent with the reslizumab appraisal (52 weeks) but did not include annual reassessment
- ICER very sensitive to response rates but the ERG did not have access to the individual patient data to validate this data
- Reslizumab and benralizumab have different mechanism of actions
  - presuming similar effectiveness and response to treatment is questionable
- ERG's clinical expert agreed with applying a constant probability of treatment discontinuation, as patients could later return to treatment the overall discontinuation rate may be lower
- ERG were unclear whether the age estimate of 50.2 (average of treatment arms in the pooled data) represented adult patients only (and not adolescents)
  - average age of UK adult patients with difficult asthma from a UK registry (Heaney et al. (2010) is 44.9 years.
  - Age is important driver in the model (ERG used 50.2 for consistency in their base case and 44.9 in scenario analysis)
- No treatment waning effect was assumed in the company submission but this should have been explored in scenario analysis

53

Please see pages 145-152 of the ERG report for more information

ERG comments-clinical inputs to model

- Mean weight reported in Heaney et al. is 81.2 (SD:19.9) kg. This is higher than mean weight of 75.2 kg included in model (and also used in the reslizumab STA)
  - ERG – higher BMI associated with severe asthma (83.1kg in ZONDA)
  - ERG preferred higher BMI and vial-based dosing scheme for reslizumab
- mOCS use at baseline in the model (54.1% in the SOC comparison and 78.6% in the mepolizumab comparison) were not reflective of UK clinical practice
  - Heaney et al. registry reported 41.7% which was used in the ERG base case for the comparison of benralizumab versus SoC
- The exclusion of the MUSCA trial from the MAIC comparing benralizumab with mepolizumab appeared contrary to the inclusion criteria:
  - when included in the MAIC analysis, after matching, [redacted]
    Effect on the base-case ICER for benralizumab vs. mepolizumab is negligible. However, when using the PAS discounted price for mepolizumab, the ICER increases **very substantially**

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Please see pages 152-161 of the ERG report for more information

ERG comments-transition probabilities

- Because exacerbations last 8 weeks in the company model, the probability of entering an exacerbation state is 4 times higher than the actual probability.
  - Reflective that probabilities used in the model must be in accordance with a 2-week cycle length
- The ERG noted that assuming exacerbation rates and proportion of responders to be the same for benralizumab and reslizumab may not be realistic in practice due to differences in biological action between the two treatments.
  - In addition the comparison between benralizumab and reslizumab only conducted on non-mOCS users due to a lack of data which further increases uncertainty
- The company did not provide individual patient level data (IPD) to the ERG, therefore treatment effectiveness analysis could not be validated by the ERG
- ERG consider the health state transition probabilities used in the company's analysis are not robust given the relatively small sample sizes used to obtain those estimates and a relatively low exacerbation rate in severe asthma patients (about one exacerbation per year)

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Please see pages 154-156 and appendix 4 of the ERG report for more information

ERG comments-asthma related mortality

- ERG notes that deaths due to asthma in people who are concordant with appropriate therapy are relatively uncommon and consider asthma related mortality was overestimated in the company's model
  - Company model predicts 1.5 times higher mortality in company base case population compared to the UK general population of the same age
- Asthma-related mortality was identified as one of the key drivers of the cost-effectiveness of the treatments (mepolizumab/reslizumab appraisals)
- The ERG identified an asthma audit report (2016) which reported the average probability of death to be 0.0078 per hospital admission. The weighted average of the probabilities of asthma death in hospital used in the company base case is ~2.5 times higher (0.01943)
- When the reduced probabilities of asthma-related death were applied to the company's model, the company base case increased by more than £2,000
  - ICER would increase further if mortality in older patients was modelled using narrower age categories.

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Please see pages 162-166 of the ERG Report for more information

ERG comments-resource use and costs

- Method to calculate cost of SoC is reasonable
- The ERG note that the mean weight of 75.2 kg used to calculate weight based acquisition cost of reslizumab is not representative of UK patients with severe asthma
  - ERG incorporate reslizumab vial-based dosing from SmPC and wastage based on the weight distribution from Haselkorn et al (83.7 kg) into their base case
- The ERG note that drug administration times used by the company did not include a period of supervision to monitor for anaphylaxis after a biologic drug has been given. ERG also note that administration of mepolizumab takes 5 mins longer than for benralizumab and 55 mins for reslizumab which was also costed approprialy by the company
  - ERG consider treatment administration costs for biological treatments are not reflective of UK clinical practice
  - Incorporating updated costs increased the ICER for benralizumab compared with SoC by ~£400. The comparisons with reslizumab and mepolizumab did not vary significantly
- Health state cycle cost were also recalculated by the ERG which had marginal effects on the ICER's for benralizumab

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Please see pages 171-181 of the ERG Report for more information

All the ICERs reported in the next slides **ONLY** include the PAS discount for benralizumab and **DO NOT** include PAS prices for the comparators mepolizumab and reslizumab

The results are therefore not representative of the true prices of the drugs- see the confidential part 2 appendix with PAS prices cost effectiveness results

ERG base case

		ICER for benralizumab compared with			
Item	**ERG changes**	**Company base case**	**SoC**	**Mepolizumab**	**Reslizumab**
1.Asthma-related mortality	assumed ~2.5 times lower than in the company's model for some patients (BTS asthma audit 2016)	See Table 60 in ERG report	£36,398	BEN dominates	BEN dominates
2.mOCS use at baseline	41.7% (Heaney et al., 2010) for all treatments	54.1% for SOC comparison,78.6% for the MEPO comparison	£36,531	BEN dominates	NA
3.Administration costs of biologics	Same administration time for mepolizumab and benralizumab assumed admin cost as in reslizumab appraisal.	Monitoring time not costed; administration of MEPO takes 5 mins longer than for BEN; 55 mins for RESLI	£34,646	BEN dominates	BEN dominates
4.Acquisition cost for reslizumab	Based on a bodyweight distribution from Haselkorn et al.,and the vial-based dosing	75.2kg	NA	NA	BEN dominates
5.Treatment discontinuation rate	0.0041/cycle (average across trials)	0.0048/cycle	£34,346	BEN dominates	BEN dominates
ERG base case (1+2+3+4+5)			**£39,135**	BEN dominates	BEN dominates

Please see pages 187-189 of the ERG report for detailed results of the base-case pair-wise analyses

ERG base-case
Results of key scenario analyses

Assumptions	ICER for benralizumab compared with:		
	SOC	MEPO	RESLI
ERG Base Case	**£39,135**	**BEN dominates**	**BEN dominates**
Set asthma-related mortality to zero	£73,560	BEN dominates	BEN dominates
mOCS use at baseline of 17% (as in Kerkhof et al. 2017)	£44,425	BEN dominates	BEN dominates
Administration costs of biologics assuming monitoring for the entire treatment duration	£40,089	BEN dominates	BEN dominates
Use EQ-5D-5L utilities from the pivotal trials directly, rather than mapped values onto EQ-5D-3L	£40,066	BEN dominates	BEN dominates
Administration costs of biologics assuming monitoring for first 16 weeks (benralizumab and mepolizumab)	£39,161	BEN dominates	BEN dominates
Patient's age at the start of treatment set to 44.9 (as in Heaney et al. (2010)	£38,340	BEN dominates	BEN dominates
Method of calculating acquisition cost of reslizumab as in the CS (RESLI comparison)	NA	NA	BEN dominates
Using results of MAIC scenario analysis for exacerbation trials including MUSCA trial (MEPO comparison)	NA	BEN dominates	NA
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	£38,246	BEN dominates	BEN dominates

Source: Table 81 (page 193) of the ERG report

Innovation
Company comments

- Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84
  - mepolizumab and reslizumab indirectly reducE the activation, proliferation, and survival of eosinophils resulting in eosinophil reduction but not depletion
- Only anti eosinophilic treatment available for administration through an accessorised prefilled syringe and convenient every 8-week dosing for SC injection
  - benralizumab reduces the number of product administration visits and associated administration costs, and facilitating home administration by where needed
  - reslizumab and mepolizumab require reconstitution before administration with high associated resource use costs

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Benralizumab for treating inadequately controlled asthma

Document B

Company evidence submission

January 2018

File name	Version	Contains confidential information	Date
Benralizumab NICE submission Document B (V1.0) 11 JAN 2018	**V1.0**	**Yes – underlined and highlighted (redacted version)**	**11 January 2018**

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Abbreviations

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AER	Annual asthma exacerbation rate
AI	Auto-injector
ALT	Alanine transaminase
AMIS	Arzneimittel-Informationssystem
APFS	Accessorised prefilled syringe
AQLQ	Asthma Quality of Life Questionnaire
AQL-5D	Asthma quality of life: 5 Dimensions
AR	Adverse reaction
AST	Aspartate transaminase
ASUI	Asthma Symptom Utility Index
ATS	American Thoracic Society
BENRA	Benralizumab
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BTS	British Thoracic Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CAE	Clinical asthma exacerbation
CDC	Centers for Disease Control and Prevention
CDR	Common Drug Review
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness curve
CEAF	Cost-effectiveness frontier
CENTRAL	Central Register of Controlled Trials
CGIC	Clinician global impression of change
CI	Confidence interval
CIC	Commercial in confidence
CIQ	Classroom Impairment Questions
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CUA	Cost-utility analysis
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DALY	Disability-adjusted life-year

DOF	Data on file
DRMI	Dropout reason-based multiple imputation
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ED	Emergency department
EMA	European Medicines Agency
EOS	Eosinophils
EPAR	European public assessment report
EQ-5D	EuroQol 5-Dimensions instrument
ER	Emergency room
ERG	Evidence Review Group
ERS	European Respiratory Society
ESS	Effective sample size
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FU	Follow-up
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General practitioner
HAS	Haute Autorité de Santé
HCP	Health care provider
HCRU	Healthcare resource use
HD	High-dose
HES	Hospital episode statistics
HIV	Human Immunodeficiency Virus
HRQOL	Health-related quality of life
HS	Health state
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IL	Interleukin
IP	Investigational product
IPD	Individual patient data
IQR	Interquartile range
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IU/L	International units per litre

IV	Intravenous
IVRS	Interactive voice-response system
KOL	Key opinion leader
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic receptor antagonist
LCI	Lower confidence interval
LOCF	Last observation carried forward
LS	Least squares
LTRA	Leukotriene receptor antagonist
LY	Life-year
LYG	Life-years gained
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
MART	Maintenance and reliever therapy
MCID	Minimum clinically important difference
MD	Mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEPO	Mepolizumab
MI	Myocardial infarction
MOA	Mechanism of action
MS	Microsoft
MTA	Multiple technology appraisal
NAEPP	National Asthma Education and Prevention Program
NA	Not applicable
NC	Not calculable
NCT	Clinical trial registry number
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Nationwide Inpatient Sample
NK	Natural killer
NMA	Network meta-analysis
NO	Nitric oxide
NR	Not reported
NRAD	National Review of Asthma Deaths
NSS	Not statistically significant
OAT	Optimised asthma therapy
OCS	Oral corticosteroid
OPCRD	Optimum Patient Care Research Database
OPRI	Observational & Pragmatic Research Institute
OR	Odds ratio
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PBAC	Pharmaceutical Benefits Advisory Committee
PDCO	Paediatric Committee at the European Medicines Agency

PEF	Peak expiratory flow
PGIC	Patient Global Impression of Change
PICOS	Population, Intervention, Comparator, Outcomes criteria
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q(X)W	Every (X) weeks
QC	Quality check
QALY	Quality-adjusted life-year
QOF	Quality outcomes framework
QOL	Quality of life
RCT	Randomised controlled trial
RESLI	Reslizumab
RR	Relative risk
RWE	Real-world evidence
SABA	Short-acting beta-agonist
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SGA	Subgroup analysis
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SOC	Standard of care
SCS	Systemic corticosteroid
SE	Standard error
SF-6D	Short-form six-dimension
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single technology appraisal
STC	Simulated treatment comparison
SUEA	Severe uncontrolled eosinophilic asthma
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTO	Time trade-off
UCI	Upper confidence interval
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
VAS	Visual analogue scale
VBA	Visual basic

WHO	World Health Organisation
WOCBP	Women of childbearing potential
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay

Executive summary

Benralizumab is a humanised monoclonal antibody with a unique mechanism of action, which is different to that of mepolizumab and reslizumab. It is the first interleukin-5 receptor (IL-5Rα) antagonist with a licence for severe uncontrolled eosinophilic asthma. By directly targeting IL-5Rα, benralizumab induces rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity; this differs from mepolizumab and reslizumab, which target IL-5 and achieve eosinophil reduction through the indirect mechanism of IL-5 neutralisation.

Benralizumab recently received a marketing authorisation for add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA in January 2018.

Three pivotal regulatory trials (SIROCCO, CALIMA and ZONDA) inform the comparison for benralizumab vs SOC. These trials have demonstrated that benralizumab is effective at reducing asthma exacerbations versus placebo when added to SOC (by 43% [RR: 0.57; 95% CI: 0.47-0.69; p<0.0001] in a pooled analysis of SIROCCO/CALIMA, and by 70% in ZONDA [nominal p<0.001]); reducing the use of oral corticosteroids (OCS) with a 75% median reduction in OCS dose compared with 25% for placebo (p<0.001), and a 4-times higher odds of achieving a reduction in OCS dose in ZONDA; and improving asthma symptoms.

AstraZeneca seeks a NICE recommendation in a subgroup of benralizumab's licensed population: patients with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months.

This is the subgroup where the key trials (SIROCCO, CALIMA and ZONDA) have demonstrated the greatest efficacy, with exacerbation reductions of 53% (p<0.001) based on pooled SIROCCO/CALIMA subgroup data in patients receiving high-dose ICS plus LABA, with blood eosinophils ≥300 cells/µl and ≥3 exacerbations in the past year, compared with placebo. In the ZONDA subgroup with blood eosinophils ≥300 cells/µl, benralizumab reduced exacerbations by [redacted], and the median percentage reduction in OCS dose was [redacted]. The proposed subgroup positioning also aligns to clinical experts' expectations of where benralizumab is likely to fit into clinical practice in NHS England and NHS Wales.

In the absence of head to head data versus mepolizumab, a matched indirect comparison (MAIC) adjusting for trial differences, [redacted]. A MAIC versus reslizumab was considered in the absence of head to head data, but was not feasible due to significant differences between trial baseline characteristics. Therefore, equivalent efficacy has been assumed for benralizumab and reslizumab in exacerbation reductions and ACQ transitions (reslizumab OCS-sparing data are currently not available).

Benralizumab requires less frequent administration (once every 8 weeks dosing after three initial doses at 4-weekly intervals) compared with mepolizumab and reslizumab, which require every 4-weekly dosing. Benralizumab is administered in a subcutaneous pre-filled syringe whereas mepolizumab and reslizumab require reconstitution before administration, with reslizumab requiring weight-based intravenous infusion. Therefore, compared with mepolizumab and reslizumab, benralizumab will require less NHS resource time for administration, and offers the advantages and convenience of less frequent administration for patients.

In the subgroup where a NICE recommendation is sought, the cost-effectiveness of benralizumab compared with standard of care therapy is estimated to be £34,284/QALY (net price with PAS), with benralizumab providing an additional [redacted] QALYs at an additional cost of [redacted] per-patient. Benralizumab dominates mepolizumab and reslizumab ([redacted] incremental QALYs and [redacted] savings versus mepolizumab; [redacted] incremental QALYs and [redacted] savings versus reslizumab), using the net price for benralizumab (including PAS) and list prices of comparators (due to confidential PAS of comparators).

Disease context and unmet needs

Asthma is a chronic, inflammatory disorder of the airways, characterised by variable airflow obstruction, airway inflammation, excessive mucus production, and airway hyper-responsiveness. Patients with asthma may present with varying degrees of severity, ranging from mild, intermittent disease to severe disease characterised by marked airflow obstruction, daily symptoms and life-threatening exacerbations (BTS/SIGN 2016, GINA 2017).

An estimated 3.6 million adults are currently receiving treatment for asthma in England (Asthma UK 2017). Despite the availability of guideline-recommended maintenance therapies (e.g., high-dose inhaled corticosteroids (ICS)/long-acting β2 agonists (LABA) with/without additional therapies such as OCS), an estimated 5%-10% of patients remain uncontrolled, with 0.8% of the UK asthma population meeting the criteria for severe uncontrolled asthma with an eosinophilic inflammatory phenotype (Kerkhof et al. 2017).

Asthma is considered severe if it remains poorly controlled, despite high dose inhaled therapies once modifiable factors such as poor inhaler technique, suboptimal adherence, or persistent environmental exposures have been excluded (BTS/SIGN 2016, GINA 2017). Patients with severe uncontrolled asthma characterised by an eosinophilic inflammatory phenotype represent those with the highest risk of exacerbations, hospitalisations, deaths, and oral corticosteroid (OCS) dependency. They have severely impaired quality of life (QoL) and are associated with substantially higher health resource use (Price et al. 2015, Kerkhof et al. 2017). For example, in the UK, the rate of exacerbations in patients with severe uncontrolled eosinophilic asthma is approximately 10 times higher than for patients without this phenotype (1.389 versus 0.132 exacerbations per patient-year, respectively) (Suruki et al. 2017). In addition, these patients can expect to have 2.5 times more GP visits, 4.1 times higher asthma-related ED attendance, 6.8 times more hospital-based specialist visits, 7.6 times more hospitalisations, and 3.9 times higher costs on average, compared with the overall asthmatic population (Kerkhof et al. 2017).

The frequent or chronic use of OCS in this group of patients is associated with short-term and long-term detrimental side effects including osteoporosis, obesity, Type 2 diabetes mellitus, and renal impairment, and an average of 43% higher associated costs when compared with patients not on maintenance OCS (O'Neill et al. 2015). A recent UK real-world study conducted by AstraZeneca found that [redacted].

More targeted therapies for severe asthma (mepolizumab, reslizumab, and omalizumab) have provided patients with important new therapeutic options. However, unmet needs still exist. Biologic treatment that specifically targets IgE (omalizumab) is not an effective treatment for patients with eosinophilic inflammation without IgE markers (EMA 2016), and has demonstrated only a limited OCS-sparing effect (Niven et al. 2016). Mepolizumab and reslizumab achieve eosinophil reduction through the indirect mechanism of IL-5 neutralisation, which results in eosinophil reduction but not depletion, and shows only variable efficacy in reducing tissue eosinophilia with no effect on the number of eosinophil progenitors in the bone marrow (NAEPP 2007, Straumann et al. 2010, Fulkerson et al. 2013, Rosenberg et al. 2013, Mukherjee et al. 2014).

Currently, available biologics for severe, eosinophilic asthma also require reconstitution before administration with associated resource use: reslizumab is administered by intravenous (IV) infusion every 4 weeks and dosing is weight-dependent, and mepolizumab is administered subcutaneously (SC) every 4 weeks (EMA 2016, AstraZeneca 2017, EMA 2017).

New targeted products are therefore needed to more effectively reduce airway eosinophilia, reduce the frequency and severity of exacerbations and hospitalisations, improve symptoms, avoid further loss of pulmonary function, reduce dependence on OCS, and limit OCS toxicity while providing dosing simplicity for patients.

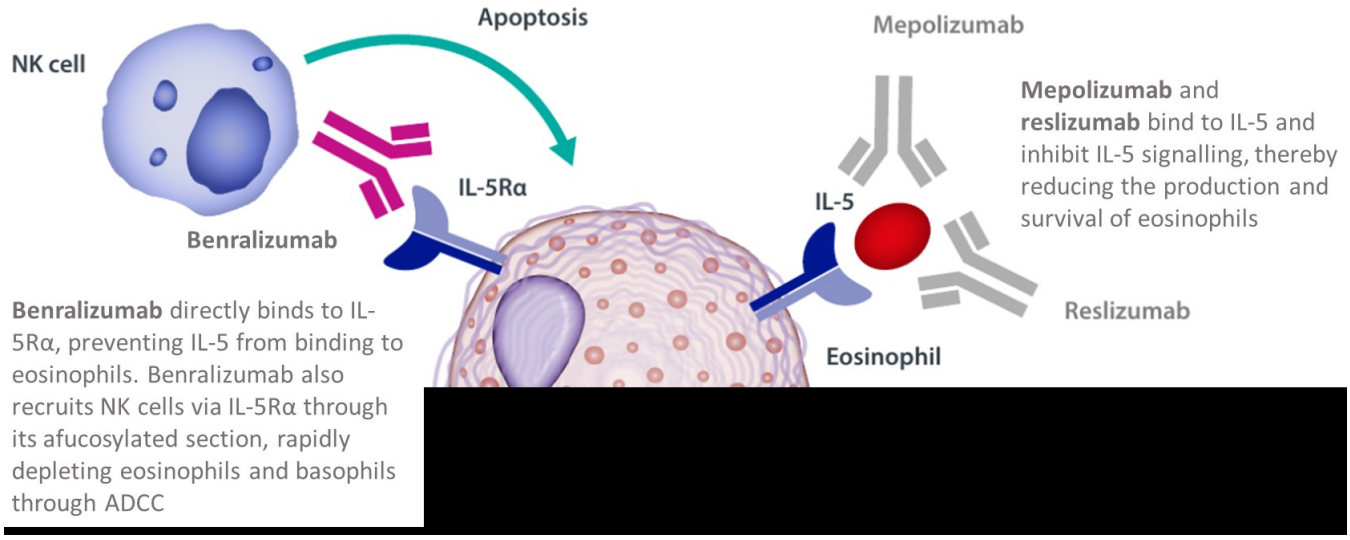
Benralizumab product information and positioning

Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA. The recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter.

As an anti-eosinophil humanised, monoclonal antibody, benralizumab specifically binds to the human IL-5 receptor alpha subunit (IL-5Rα), with a unique mode of action. By binding to eosinophils through IL-5Rα, benralizumab blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil. Additionally, due to an afucosylated section on the molecule itself, benralizumab increases the affinity of eosinophils to Natural Killer (NK) cells. This leads to a rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in a systemic efficacy response (Laviolette et al. 2013). Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84 (Laviolette et al. 2013).

In contrast, mepolizumab and reslizumab act by binding to IL-5 and inhibiting IL-5 signalling, thereby indirectly reducing the activation, proliferation, and survival of eosinophils (Figure 1) – this ultimately results in eosinophil reduction but not depletion.

Figure 1: Mode of action of benralizumab



ADCC: Antibody-dependent cell-mediated cytotoxicity; IL-5: Interleukin 5; IL-5R: Interleukin 5 receptor; NK: Natural killer

Currently, benralizumab is the only anti-eosinophilic treatment available with simple administration via an accessorised prefilled syringe and every 8-week SC dosing. Mepolizumab and reslizumab require reconstitution before administration, and more frequent dosing (weight-based every 4 weeks IV dosing as an infusion for reslizumab, fixed every 4 weeks SC dosing for mepolizumab). The simple dosing schedule for benralizumab may therefore reduce the humanistic and economic burden of severe asthma through lower resource use.

In this submission, a recommendation for benralizumab is sought in the subpopulation of patients with severe eosinophilic asthma who are inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per µl AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months. The proposed subgroup reflects where benralizumab is anticipated to provide the most clinical benefit, based on Phase 3 trial data and clinical opinion on the positioning of anti-IL-5 medicines in UK practice (Bleecker 2016, FitzGerald 2016, AstraZeneca 2017, Nair et al. 2017).

Benralizumab will meet an unmet clinical need in this patient population through its innovative mechanism of action, strong clinical efficacy and tolerability (described below), and robust OCS-sparing effect, as well as a less frequent dosing schedule than mepolizumab and reslizumab.

Key clinical evidence for benralizumab

The key evidence to support the effectiveness of benralizumab in severe asthma is based on three pivotal Phase 3 placebo-controlled clinical trials (SIROCCO, CALIMA, and ZONDA) (Bleecker 2016, FitzGerald 2016, Nair et al. 2017), and a matched-adjusted indirect comparison (MAIC) versus mepolizumab.

Intent-to treat (ITT) data versus standard of care (SOC)

Throughout the Phase 3 clinical trial programme, benralizumab demonstrated statistically significant reductions in the annual exacerbation rate compared with placebo in the overall ITT analyses, when added to standard of care therapy (medium or high-dose ICS plus LABA) (Table 1).

Further, improvements were consistently observed for key secondary endpoints, including those relating to lung function (i.e. FEV_1) and PRO measures (e.g. total asthma symptom score and quality of life measures), versus placebo.

In addition, benralizumab reduced patients' exposure to and dependence on chronic OCS; benralizumab was associated with a 75% median reduction in daily OCS dose in the ZONDA trial, compared with 25% for placebo, and a 4-times higher odds of achieving a reduction in median daily OCS dose (Table 1).

Table 1: Summary of key efficacy results for benralizumab Q8W in the pivotal Phase 3 trials (ITT population)

Study name, NCT number, and overall study sample size	Study objective	Key efficacy outcomes for benralizumab Q8W versus placebo, ITT analysis		
		Reduction in annual exacerbation rate	Prebronchodilator FEV_1 (L)	Total asthma symptom score*
SIROCCO (NCT01928771) N=1,205	Efficacy and safety study of benralizumab added to high-dose ICS plus LABA in patients with uncontrolled asthma	51% reduction RR: 0.49 (95% CI: 0.37 - 0.64; p<0.0001)	159ml improvement LS mean difference: 0.159 (95% CI: 0.068 - 0.249; p=0.0006)	0.25 point decrease LS mean difference: −0.25 (95% CI: −0.45 to −0.06; p=0.0118)
CALIMA (NCT01914757) N=1,306	Efficacy and safety study of benralizumab added to medium-dose or high-dose ICS plus LABA in patients with uncontrolled asthma	28% reduction RR: 0.72 (95% CI: 0.54 - 0.95; p=0.0188)	116ml improvement LS mean difference: 0.116 (95% CI: 0.028 - 0.204; p=0.0102)	0.23 point decrease LS mean difference: −0.23 (95% CI: −0.43 to −0.04; p=0.0186)
ZONDA (NCT02075255) N=220		70% reduction RR: 0.30 (95% CI: 0.17 - 0.53; p<0.001)	112ml improvement LS mean difference: 0.112 (95% CI: -0.033 - 0.258; p=0.129)	0.18 point decrease LS mean difference: -0.18 (95% CI: -0.51, 0.16; p=0.291)

	Reducing OCS use in patients with uncontrolled asthma on high dose ICS plus LABA and chronic OCS therapy	**Median % reduction in final daily OCS dose:** 75% reduction versus 25% reduction for placebo (p<0.001) (Median treatment difference of 37.50%; 95% CI: 20.80, 50.00) **Odds of a reduction in OCS dose:** 4 times higher OR: 4.12 (95% CI 2.22, 7.63; p<0.001) **Discontinuation of OCS in eligible patients^:** 52% of benralizumab-treated patients vs 19% placebo-treated patients (p=0.002).

* A decrease in score suggests an improvement

^ Patients eligible for a 100% reduction in OCS dose (i.e. OCS discontinuation) were those receiving ≤12.5mg/day at the end of the run-in phase

Differences in trial methodology should be considered when interpreting results presented in this table

Reductions in exacerbation rates appeared to be greater in SIROCCO (51%) than in CALIMA (28%), which is likely to be driven by regional differences in baseline exacerbation history (i.e., patients in CALIMA had less severe disease in terms of exacerbation rates at baseline, which led to a strong placebo response, and a lower rate of exacerbations during the study, regardless of treatment arm).

In terms of safety outcomes, benralizumab was found to be well tolerated, with rates of AEs, serious AEs, and AEs leading to discontinuation of treatment being similar between the benralizumab and placebo groups. Most AEs were mild to moderate in intensity, and not considered to be related to treatment.

Subgroup data versus SOC

The similar trial designs of SIROCCO and CALIMA allowed the results in patients receiving high-dose ICS plus LABA to be pooled, to increase the effective sample size, better characterise the relationship between the clinical efficacy of benralizumab and characteristics such as baseline blood eosinophil counts and exacerbation history, and therefore identify which patients are most likely to benefit from treatment with benralizumab.

Based on the results of the pooled analysis, benralizumab was found to be more efficacious in patients with blood eosinophils ≥300 cells/μL and a history of three or more exacerbations in the previous year (compared with patients with lower eosinophil counts and less frequent exacerbations). In these patients, benralizumab was found to significantly reduce the annual asthma exacerbation rate by 53% (p<0.001), improve FEV_1 from baseline by 254 ml (p<0.001), and improve the ACQ-6 score from baseline by -0.43 points (p=0.002) compared with placebo, when both were added to standard of care therapy (Table 2) (AstraZeneca data on file 2017).

Table 2: Efficacy of benralizumab in the pooled SIROCCO and CALIMA subgroup analysis

Estimate	Benralizumab 30mg Q8W (N=123)	Placebo (N=136)	Difference between arms
Marginal annual exacerbation rate	0.85	1.83	RR: 0.47 (95% CI: 0.32, 0.67); p<0.001
FEV_1 pre-bronchodilator change from baseline (L)	0.485	0.231	Estimate for difference: 0.254 (95% CI: 0.113, 0.395); p<0.001
ACQ-6 score change from baseline	-1.59	-1.16	Estimate for difference: -0.43 (95% CI: -0.69, -0.16); p=0.002
Mean EQ-5D-5L score change from baseline	0.10	0.06	Estimate for difference: 0.04 (95% CI: 0.01, 0.08); p=0.019

In a subgroup analysis of patients from ZONDA with blood eosinophils ≥300 cells/µl, [redacted] compared with a treatment difference of 37.5% in the ITT population) (Table 3).

Table 3: Efficacy of benralizumab in the ZONDA subgroup analysis (patients with blood eosinophils ≥300 cells/µL)

Estimate, 95% CI	Benralizumab 30mg Q8W (N=61)	Placebo (N=64)	Difference between arms
Percent reduction in OCS dose, median (95% CI)	[redacted]	[redacted]	[redacted]
Annual exacerbation rate	[redacted]	[redacted]	[redacted]
FEV1 pre-bronchodilator change from baseline (L)	[redacted]	[redacted]	[redacted]
AQLQ(S)+12 score change from baseline	[redacted]	[redacted]	[redacted]

* Hodges-Lehman median treatment difference

As discussed above, a NICE recommendation is therefore sought in the subgroup of patients with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS (≥ 800µg FP daily) plus LABA, with a blood eosinophil count ≥300 cells per µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months.

Data versus mepolizumab and reslizumab

In the absence of head-to-head trials against the comparators mepolizumab and reslizumab, the feasibility of conducting an indirect comparison was assessed. Cross-trial differences were too large to conduct a robust network meta-analysis (NMA), and a population-adjusted

ITC approach, specifically a matching-adjusted indirect comparison (MAIC), was therefore considered to adjust for cross-trial differences in the overall clinical trial patient population. A MAIC was feasible versus mepolizumab, which found [redacted]

Table 4: Summary of MAIC results for benralizumab versus mepolizumab

Studies	Endpoint comparison	Benralizumab vs. mepolizumab (matched):	
SIROCCO/ CALIMA vs. MENSA/ DREAM*	Annualised rate of clinically significant exacerbations, RR (95% CI)	[redacted]	[redacted]
	FEV_1 at week 32, mean difference (95% CI)	[redacted]	[redacted]
	Annualised exacerbation rate leading to ER/hospitalisation, RR (95% CI)	[redacted]	[redacted]
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]

* High-dose ICS populations (≥ 880 µg FP daily SIROCCO/CALIMA vs MENSA/DREAM) adjusted for trial differences.
^ High-dose ICS populations (>500 µg FP daily ZONDA vs SIRIUS) adjusted for trial differences.
MAIC includes benralizumab 30 mg Q8W SC data vs mepolizumab 100mg Q4W SC [& 75mg Q4W IV (bioequivalent dose) in MENSA/DREAM] data

For the comparison between benralizumab and reslizumab, there was high heterogeneity between trial baseline characteristics (resulted in a 99% reduction in the effective sample size (ESS=20)), meaning that a robust MAIC was not feasible. As such; equivalent efficacy has been assumed for benralizumab and reslizumab in exacerbation reductions and ACQ transitions for this submission (OCS-sparing data for reslizumab are not currently available).

[redacted] benralizumab may provide additional benefit in patients requiring maintenance OCS; this may be explained by the unique mechanism of action of benralizumab, which leads to near complete elimination of eosinophils from the airways.

Economic impact of benralizumab

No economic analyses that were designed to assess the cost-effectiveness of benralizumab were identified; therefore, a *de novo* model was developed. A Markov model was selected as the preferred structure for the model, utilising a 2-week cycle length, with a lifetime time horizon. A discount rate of 3.5% was applied to costs and outcomes, and the perspective was that of the UK NHS and personal and social services, in line with the NICE reference case.

Asthma states in the model were based on the control status of asthma as defined by ACQ-6 score criteria, with a threshold for controlled asthma of below 1.5 and a threshold for uncontrolled asthma above 1.5. Since asthma is a variable disease, patients could transition between controlled and uncontrolled health states every 2 weeks, transition probabilities for which were calculated directly from the trial data, where ACQ was captured on a 2-weekly basis.

During each cycle, patients were also at risk of exacerbations; this risk was also calculated directly from the trial data and separately for the controlled and uncontrolled states. Following an exacerbation, patients could either experience a further exacerbation or return to the controlled/uncontrolled states. Patients were at risk of all-cause mortality at all times, probabilities for which were derived from life tables. There was an additional mortality risk associated with an exacerbation, which was calculated following similar methodology to that employed in other NICE appraisals of asthma biologics (mepolizumab and reslizumab), using The National Review of Asthma Deaths (NRAD) plus literature sources from Watson et al and Roberts et al.

A stopping rule was included in the model at 12 months based on a patient's exacerbation rate and/or reduction in OCS dose; patients who had a clinically meaningful reduction in at least one of these outcomes continued on benralizumab, while those who did not discontinued benralizumab and reverted to standard of care.

All patients who responded to benralizumab were assumed to continue benralizumab for the rest of their lifetime, whilst facing an annual risk of discontinuation, and treatment effect was extrapolated accordingly.

Utility in the model was applied to all model asthma health states, using mapped EQ-5D-3L from EQ-5D-5L from SIROCCO/CALIMA and AQLQ-12 from ZONDA. An event-based approach to resource use was adopted for acute events. UK unit costs were applied in the model.

Based on the results of this analysis, the cost-effectiveness of add-on benralizumab (+PAS) compared with SoC alone was calculated to be £34,284/QALY gained in the base case population, with benralizumab providing an additional [redacted]QALYs at an additional cost of £[redacted]per-patient (net price with PAS).

Add-on benralizumab was dominant versus add-on mepolizumab, with QALY gain of [redacted]and cost saving of £[redacted]in the mepolizumab NICE-recommended population. Similarly, add-on benralizumab was dominant versus add-on reslizumab, with QALY gain of [redacted] and cost saving of £[redacted]in the reslizumab NICE-recommended population. However, it should be noted that these values are based on comparisons of benralizumab net price with mepolizumab and reslizumab list prices due to a confidential PAS being in place for both of these medicines.

The key strength of the model is that it is reflective of the two dimensions of asthma: symptoms and exacerbations, based on a consistent common source for benralizumab and SoC (the benralizumab SIROCCO, CALIMA and ZONDA trials). Further to this, to address concerns during the mepolizumab NICE STA that the burden of OCS was not fully captured within the model, we have generated new UK real-world evidence demonstrating the risk of comorbidities associated with maintenance OCS therapy, specifically for asthma patients in the UK, and have applied this within the model. Key limitations relate to uncertainties generated by the MAIC comparison, lack of long-term data related to asthma-related morbidity and mortality, potential underestimation of the long-term costs and consequences of chronic OCS use, and the necessity of using a net versus list price comparison owing to confidential PAS's for both mepolizumab and reslizumab. The model was most sensitive to the starting age of the cohort (as mortality varies with age) in the comparison versus SOC, and to the proportion of responders to treatment and risk of discontinuation of add-on therapy in the comparison versus mepolizumab. Varying most other inputs had a minor impact on the ICERs when tested in sensitivity analysis.

The net budget impact for benralizumab has been estimated to be [redacted]in year 1, increasing to [redacted]in year 5.

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

Summary of key points

- Despite treatment with the current standard of care (high-dose ICS plus LABA with/without additional therapies such as OCS), a proportion of patients with severe asthma remain uncontrolled and at high risk.
- Patients with severe uncontrolled asthma characterised by an eosinophilic phenotype represent a minority of asthma patients with the highest risk of exacerbations, hospitalisations, and OCS dependency. They have severely impaired QoL, and are associated with substantially higher healthcare resource utilisation and an increased risk of death compared with the overall asthmatic population.
- Additionally, these patients are frequent or chronic users of OCS, which is associated with short-term and long-term detrimental side effects such as obesity, diabetes, osteoporosis, and peptic ulcerations, and an average of 43% higher associated costs when compared with patients not on maintenance OCS.
- A recent UK real-world study conducted by AstraZeneca found that exposure to OCS in asthma patients resulted in a [redacted], compared with patients not exposed to OCS after adjustment
- New, targeted therapies are therefore needed to reduce the frequency and severity of exacerbations and hospitalisations, improve symptoms, avoid further loss of pulmonary function, reduce OCS dependency, and limit drug toxicity while providing dosing simplicity and convenience for patients
- Benralizumab is a humanised, monoclonal antibody with an innovative and unique mechanism of action. By targeting the IL5 receptor, benralizumab induces rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity; this differs from anti-IL-5 antibody products that achieve eosinophil reduction through the indirect mechanism of IL-5 neutralisation (e.g. mepolizumab, reslizumab)
- Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA

- Benralizumab is the only anti-eosinophilic treatment available with administration via an accessorised prefilled syringe by a healthcare provider, for subcutaneous injection and convenient every 8-week dosing.
- Benralizumab rapidly depletes blood eosinophils following the first dose, with a prolonged duration of effect.
- A NICE recommendation is sought in the subgroup of patients with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per µl AND ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months

B.1.1 Decision problem

This submission focuses on part of the technology's marketing authorisation; a NICE recommendation is sought for the subgroup of adults with severe eosinophilic asthma that is inadequately controlled, despite high-dose inhaled corticosteroids (ICS) (≥ 800µg FP daily) plus long acting β-agonists (LABA) with:

- A blood eosinophil count that has been recorded as 300 cells per microlitre or more

AND either

- 3 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months

OR

- Treatment with continuous oral corticosteroids over the previous 6 months

The proposed subgroup positioning is narrower than the full marketing authorisation, as this reflects where benralizumab provides the most clinical benefit based on Phase 3 trial results, and is in line with UK clinical experts' views on the positioning of anti-IL-5 medicines in the clinical treatment pathway (AstraZeneca 2017). Benralizumab will fit into the existing NICE asthma pathway within the 'difficult or severe asthma' patient category under the 'asthma management' section.

Table 5. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with severe asthma with elevated blood eosinophils	Adults with severe eosinophilic asthma that is inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists with: • A blood eosinophil count that has been recorded as 300 cells per microlitre or more AND either • 3 or more asthma exacerbations needing systemic corticosteroids in the past 12 months OR • Treatment with continuous oral corticosteroids over the previous 6 months	This subpopulation reflects where benralizumab provides the most clinical benefit based on the trial data, and is in line with clinical experts' views on the positioning of anti-IL-5 medicines in the clinical treatment pathway. Patients who are within licence but not covered by this subgroup: those with <300 eosinophils per µl, as well as those with ≤2 exacerbations in the past 12 months or not requiring continuous OCS use for the past 6 months
Intervention	Benralizumab as an add-on to optimised standard therapy	Benralizumab as an add-on to optimised standard therapy (high dose inhaled corticosteroids and long acting beta-2 agonist with or without oral corticosteroids and other asthma controllers)	N/A
Comparator(s)	• Optimised standard therapy • Reslizumab (in addition to optimised standard therapy) • Mepolizumab (in addition to optimised standard therapy)	• Optimised standardised therapy (high-dose inhaled corticosteroid and long acting beta-2 agonist with or without oral corticosteroids and other asthma controllers) • Reslizumab (in addition to optimised standard therapy) • Mepolizumab (in addition to optimised standard therapy) In line with the conclusions of the appraisal committees for mepolizumab and reslizumab, as well as the final Scope for this appraisal, omalizumab was not considered to be an appropriate comparator.	N/A

Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • clinician evaluation of response • lung function • mortality • discontinuation • adverse effects of treatment • health-related quality of life.	Patient evaluation of response not available in the trial data Discontinuation is treated as a constant rather than a time dependent variable as is consistent with other appraisals in severe asthma.
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.	An overview of the cost-effectiveness model follows: A Markov model has been selected as the preferred structure for the model. The model utilises a 2 week cycle length, with a lifetime time horizon. A default discount rate of 3.5% will be applied to costs and outcomes. **Health States:** Asthma states in the model are based on the control status of asthma (controlled, uncontrolled) as defined by Asthma Control Questionnaire (ACQ) score criteria. The threshold for controlled asthma is below 1.5 and the threshold for uncontrolled asthma is above 1.5. **Transitions:** Since asthma is a variable disease, patients can transition between controlled and uncontrolled health states every 2 weeks. This transition probability is calculated directly from the trial data where ACQ was captured on a 2 weekly basis.	N/A – model aligns with reference case

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	During each cycle, patients are also at risk of exacerbations; this risk is also calculated directly from the trial data separately for the controlled and uncontrolled states. Following an exacerbation patients can either have a further exacerbation or return to the controlled/uncontrolled states. Patients are at risk of all-cause mortality at all times with this probability coming from life tables. There is an additional mortality risk associated to an exacerbation which is calculated as per previous appraisals' (mepolizumab and reslizumab) preferred assumptions using NRAD plus literature sources from Watson et al and Roberts et al. **Treatment duration:** A stopping rule is included in the model at 12 months based on a patient's exacerbation rate and/or reduction in OCS dose, patients who meet these criteria continue on benralizumab, those that do not revert to standard of care. All patients are assumed to continue benralizumab for the rest of their lifetime and the treatment effect is extrapolated accordingly, discontinuation is included in the model on a yearly basis and these patients revert to standard of care. **Utilities:** Utility in the model is applied to the model asthma health states using mapped EQ-5D-3L from EQ-5D-5L from SIROCCO/CALIMA and AQLQ-12 from ZONDA, with a decrement applied to those patients who suffer an exacerbation during each cycle. **Resource use and costs:** The model adopts the perspective of the UK NHS and personal and social services. An event based approach to resource use is adopted for acute events. UK unit costs are applied in the model. The model facilitates both deterministic analysis and probabilistic sensitivity analysis. The proposed PAS for benralizumab has been taken into account (while list prices for mepolizumab and reslizumab have been used due to the confidential nature of the PAS for these comparators)	

Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • baseline eosinophil levels (further detail not specified) • people who require maintenance oral corticosteroid treatment • people who require frequent oral corticosteroid treatment. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The submission focuses on part of the technology's marketing authorisation; a NICE recommendation is sought for the subgroup of adults with severe eosinophilic asthma that is inadequately controlled, despite high-dose inhaled corticosteroids (ICS) (≥ 800µg FP daily) plus long acting β-agonists (LABA) with: • A blood eosinophil count that has been recorded as 300 cells per microlitre or more AND either • 3 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months OR • Treatment with continuous oral corticosteroids over the previous 6 months	The proposed subgroup positioning is narrower than the full marketing authorisation, as this reflects where benralizumab provides the most clinical benefit based on Phase 3 trial results, and is in line with UK clinical experts' views on the positioning of anti-IL-5 medicines in the clinical treatment pathway (AstraZeneca 2017a)
Special considerations including issues related to equity or equality	-	None	-

B.1.2 Description of the technology being appraised

Table 6 includes a summary of the key product attributes of benralizumab. The summary of product characteristics and European public assessment report are presented in Appendix C.

Table 6: Summary of the technology being appraised

UK approved name and brand name	Benralizumab (Fasenra™)
Mechanism of action	Benralizumab is an anti-eosinophil humanised, monoclonal antibody that specifically binds to the human IL-5 receptor alpha, which is expressed on eosinophils and basophils in humans. Benralizumab induces rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity by targeting the IL-5 receptor. Depletion of eosinophils is reversible following cessation of benralizumab therapy. Benralizumab has a unique mode of action. By recruiting natural killer cells via IL-5Rα, benralizumab actively targets and depletes eosinophils. Binding to eosinophils through IL-5Rα blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil. This provides differentiation from anti-IL-5 antibody products that achieve eosinophil reduction through the indirect mechanism of IL-5 neutralisation (mepolizumab, reslizumab), which results in eosinophil reduction, but not depletion.
Marketing authorisation/ CE mark status	Marketing authorisation was received in January 2018
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.
Method of administration and dosage	Benralizumab is administered as a 30 mg dose, once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by SC injection. Benralizumab is the only anti eosinophilic treatment available for SC injection through an accessorised pre-filled syringe (APFS – no reconstitution required) with convenient 8-weekly dosing, reducing the number of product administration visits and associated administration costs, and facilitating home administration by a HCP, where needed. Benralizumab should be prescribed by physicians experienced in the diagnosis and treatment of severe asthma.
Additional tests or investigations	None
List price and average cost of a course of treatment	List price is £1955/vial (30 mg SC injection) Treatment duration is lifetime.
Patient access scheme (if applicable)	A simple PAS has been submitted to PASLU: net price [redacted] (30 mg SC injection).

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

B.1.3.1 Disease burden

Asthma

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. The disease is characterised by widespread, variable, and reversible airflow obstruction; airway inflammation; excessive mucus production; and airway hyper-responsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (BTS/SIGN 2016). Progressive pathologic airway remodelling and scarring may occur in persistent asthma, resulting in partially reversible or irreversible airway obstruction (Pascual et al. 2005). Asthma comprises distinct 'endotypes', most notably T helper 2 (T_H2)-low and -high. T_H2-high asthma is characterised by increased airway and systemic eosinophilia, and the disease is more severe than in T_H2-low asthma (Fahy 2015).

Severe asthma

Asthma presents with varying degrees of severity, ranging from mild, intermittent disease to severe presentations with life-threatening exacerbations. The definition of asthma severity has evolved from symptom-based to one that is focused on the intensity of treatment required to achieve good asthma control (BTS/SIGN 2016, GINA 2017). Asthma is considered severe if it is poorly controlled despite the elimination of modifiable factors (e.g., poor inhaler technique/ suboptimal adherence, persistent environmental exposures) and the correct use of optimised standard therapy (BTS/SIGN 2016, GINA 2017).

Severe uncontrolled asthma

While the majority of asthma patients can be adequately controlled with the current SoC (high-dose ICS plus LABA with or without OCS and other asthma controllers, as recommended by national guidelines - NICE and BTS/SIGN), a subset of patients with severe asthma remains uncontrolled (BTS/SIGN Steps 4 and 5) and are associated with poor outcomes. These patients represent a major unmet need (Gauthier et al. 2015).

Evidence for any one of the following four criteria while on current high-dose therapy identifies the patient as having "severe asthma" (Chung et al. 2014):

1. Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5 or Asthma Control Test (ACT) <20 (or "not well controlled" by National Asthma Education and Prevention Program [NAEPP;(NAEPP 2007)] or GINA guidelines over the 3 months of evaluation)
2. Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year
3. Serious exacerbations: at least 1 hospitalisation, Intensive Care Unit (ICU) stay, or mechanical ventilation in the previous year
4. Airflow limitation: FEV_1<80% predicted (in the presence of reduced FEV_1/FVC defined as less than the lower limit) following a withhold of both short- and long-acting bronchodilators

These criteria were also used to determine eligibility in the benralizumab Phase 3 trials. Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma (Chung et al. 2014).

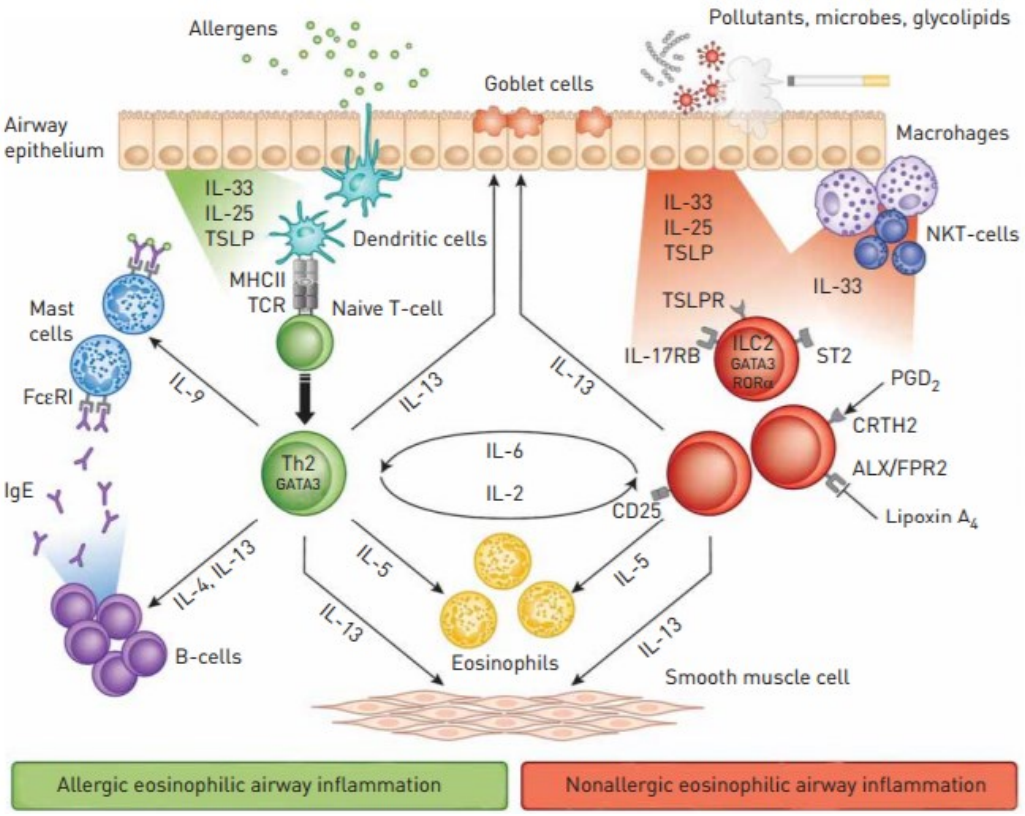
Eosinophilic phenotype of asthma

The inflammatory characteristics of asthma have been classified into 4 distinct phenotypes based on the cellular airway inflammatory responses that include (1) eosinophilic, (2) neutrophilic, (3) mixed granulocytic (eosinophilic and neutrophilic), and (4) paucigranular (Simpson et al. 2006). There are observed variabilities in clinical response to currently available asthma therapies, which appear to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012, Gauthier et al. 2015).

Eosinophilic inflammation is common in asthma (Garcia et al. 2013, Schleich et al. 2013), with approximately 50% of all patients with asthma having eosinophilic inflammation (Zhang et al. 2007).

Eosinophilic inflammation is an important component in the pathogenesis of asthma. Eosinophils release pro-inflammatory mediators, which contribute to epithelial cell damage, airway hyper-responsiveness, mucus hypersecretion, and airway remodelling (Patterson et al. 2015). Eosinophilic airway inflammation can be both allergic and non-allergic in aetiology, with high eosinophil levels associated with more severe forms of asthma (GINA 2017). Eosinophils are recruited to the airways and activated in response to inflammatory stimuli. Interleukin-5 (IL-5) is the major cytokine promoting eosinophil proliferation and activation (Figure 2) (de Groot et al. 2015).

Figure 2. Two different pathways that lead to eosinophilic airway inflammation in asthma



Source: (de Groot et al. 2015)

Apart from elevated numbers of eosinophils in sputum and peripheral blood, adults with an eosinophilic phenotype can be clinically identified by typical characteristics. Features common in uncontrolled eosinophilic asthma include (de Groot et al. 2015):

- Frequent exacerbations
- Chronic rhinosinusitis (inflammation of the nasal mucous membrane) with nasal polyposis
- Persistent airflow limitation and air trapping
- Poor asthma control
- Dependence on OCS

Epidemiology

Asthma affects people of all ages, including 3.6 million adults in England alone (Asthma UK 2017). A recently published cohort study using CPRD/OPCRD data (N=401,261) aimed to characterise burden of severe, uncontrolled, eosinophilic asthma in the UK. An estimated 7% of patients meeting the study eligibility criteria (i.e., active asthma without concurrent COPD and with recorded EOS count) had experienced two or more exacerbations during the baseline year; 10% had received high-dose ICS plus LABA during both baseline and outcome years; and 1.7% received high-dosage ICS plus LABA during both baseline and outcome years and also experienced two or more attacks during the baseline year. Overall, 0.81% (95% CI 0.78% to 0.84%) of the asthmatic population met the study definition of severe uncontrolled eosinophilic asthma, namely high-dosage ICS plus LABA in both baseline and outcome years, two or more attacks in the baseline year, and high blood eosinophil count of $\geq 0.3 \times 10^9$/L at the index date (Kerkhof et al. 2017).

Based on a sub-analysis of this study, approximately 1.7% of the total asthma population would meet the anticipated NICE recommended population for benralizumab (i.e. blood eosinophil count ≥300 cells/μl in the previous 12 months, and either ≥3 asthma exacerbations needing OCS in the previous 12 months or treatment with continuous OCS over the previous 6 months). This would equate to 63,589 patients when this percentage is applied to the 2016 asthma QOF register for England and Wales (AstraZeneca data on file 2017).

In 2015, 1,468 people died due to asthma in the UK, the highest level for over 10 years (Asthma UK 2016).

Burden of severe uncontrolled eosinophilic asthma

Clinical burden

Exacerbations of asthma are episodes characterised by a progressive increase in symptoms of shortness of breath, coughing, wheezing, chest tightness, and progressive decrease in lung function, i.e., they represent a change from the patient's usual status that is sufficient to require a change in treatment. Severe exacerbations are potentially life-threatening and their treatment requires careful assessment and close monitoring (GINA 2017).

Patients with severe uncontrolled asthma are at a higher risk of exacerbations, hospitalisation, and death compared with patients with controlled asthma, and are often dependent on OCS (Heaney et al. 2010). CPRD data have shown that in the UK, the rate of exacerbations in patients with severe uncontrolled asthma is approximately 10 times higher than for patients without (1.088 versus 0.098 exacerbations per patient-year, respectively) (Suruki et al. 2017).

Increased eosinophils are also associated with increased severity, more exacerbations, less well-controlled disease, decreased lung function, higher mortality, and higher OCS dependency in patients with asthma (Hospers et al. 2000, de Groot et al. 2016, Price et al. 2016). For example, a UK CPRD/OPCRD study found that the risk of experiencing a severe exacerbation was significantly higher (RR: 1.30, 95% CI: 1.23–1.37) for patients with eosinophil counts >300 cells per μL compared with counts of 300 cells per μL or less (Price et al. 2015).

In patients at GINA Step 4 or 5 with ≥2 prior exacerbations in the past 12 months, and eosinophilic asthma, the annual rate of exacerbations was estimated to be 10 times higher than in asthmatic patients not meeting these criteria (1.389 versus 0.132 exacerbations per patient-year, respectively) (Suruki et al. 2017).

Humanistic burden

Patients with asthma have impaired quality of life which can lead to fatigue, absence from school or work and psychological problems including stress, anxiety and depression (Accordini et al. 2006). QoL detriments are usually captured using instruments including the asthma-specific ACQ, AQLQ, and ACT (Table 7), as well as generic instruments such as the EQ-5D, although additional assessments may be required for themes such as asthma-related tiredness, which are not typically reported in the standardised assessments.

Table 7: Comparison of disease-specific, validated PRO measures commonly used to assess quality of life in asthma

PRO measure	Description	Scoring	Minimally important difference
Asthma Control Questionnaire (ACQ)	7-item questionnaire to assess daytime and night-time symptoms, FEV1, and rescue β2-agonist use; 5 and 6-item versions (ACQ-5 and 6) also available	Items scored on a 0-7 scale, with low numbers representing better control. Total scores range from 0 (totally controlled) to 6 (severely uncontrolled)	A change in score of 0.5
Asthma Quality of Life Questionnaire (AQLQ)	32-item questionnaire to assess asthma-related quality of life across the domains of symptoms, activity limitations, emotional function, and environmental exposure	Items scored on a 1-7 scale, with low numbers indicating worse quality of life. Total scores range from 1 (severely impaired) to 7 (not impaired at all)	A difference of 0.5 for overall quality of life and for each of the individual domains
Asthma Control Test (ACT)	5-item questionnaire to identify patients with poorly controlled asthma, across domains of symptoms, rescue medication use, daily functioning, and self-assessed asthma control	Items scored on a 1-5 scale, with lower numbers representing worse asthma control. Total scores range from 5-25, with scores >19 indicating well-controlled asthma	3 points between two groups or for changes over time

PRO: patient-reported outcome

Quality of life decreases with increasing severity of disease. Compared with patients with moderate-severe controlled disease, patients with severe uncontrolled asthma:

- experience more symptoms, night time awakenings, rescue medication use, activity impairment, and worse QoL compared with those who are controlled (Bateman et al. 2007, Chen et al. 2007, Xu et al. 2017);
- had higher ACQ scores (mean 3.8 vs. 2.4, respectively) (Quirce et al. 2011) and lower ACT scores (mean 17 vs. 24) (Novelli et al. 2015), indicating poorer asthma control; and
- had lower AQLQ scores (mean 3.5 vs. 4.8, respectively) (Quirce et al. 2011), indicating worse QoL

Further, a large European survey (N=8000) reported that 91.7% of uncontrolled asthma patients had symptoms that affected normal daily activities at least 1 day per week, compared with 0% of controlled asthma patients (Price et al. 2014).

Economic burden

Although patients with severe uncontrolled asthma comprise a small proportion of the total asthma population, they have substantially more healthcare resource use (HCRU) than patients with moderate or mild asthma (O'Neill et al. 2015).

Analysis of UK CPRD/OPCRD data has found that patients with severe uncontrolled eosinophilic asthma have 2.5 times more GP visits, 4.1 times higher asthma-related ED attendance, 6.8 times more hospital-based specialist visits, and 7.6 times more hospitalisations, on average, compared with the overall asthmatic population (Table 8) (Kerkhof et al. 2017).

This increased resource use leads to increased costs; for example in this UK CPRD/OPCRD study, total mean asthma-related costs were found to be £861 per year for patients with severe uncontrolled eosinophilic asthma, compared with £222 for the main study population (i.e., the general asthma population), representing a cost ratio of 3.9 (95% CI: 3.7 - 4.1) (Table 8) (Kerkhof et al. 2017).

Table 8: Mean asthma-related HCRU, associated direct costs (in 2015 £), and cost ratios for patients with SUEA compared with the overall UK asthma population, per year

Outcome, mean (SD)	All patients (n=363558/146485*)	SUEA (n=2940/1206*)	HCRU and cost ratios
GP visit‡			
Number	1.36 (1.57)	2.67 (2.80)	2.5 (2.4 to 2.6)

Costs	£30.8 (49.8)	£77.0 (107.5)	
Hospital-based specialist visit			
Number	0.04 (0.33)	0.30 (0.96)	6.8 (6.0 to 7.7)
Costs	£6.9 (52.2)	£46.7 (149.2)	
Asthma-related ED attendance			
Number	0.01 (0.11)	0.04 (0.25)	4.1 (3.2 to 5.3)
Costs	£1.6 (18.8)	£6.6 (44.7)	
Hospitalisation*			
Number	0.01 (0.12)	0.05 (0.38)	7.6 (4.7 to 11.6)
Costs	£10.4 (194.7)	£78.7 (660.3)	
Medication cost	£170.1 (218.2)	£645.4 (285.4)	3.8 (3.7 to 3.9)
Total costs*	£222.0 (337.2)	£861.0 (811.9)	3.9 (3.7 to 4.1)

*The first number in the column headers represents the total number of patients in the CPRD dataset. The second number represents those patients in the Clinical Practice Research Datalink who also had linked Hospital Episode Statistics (HES - a data warehouse containing more complete and reliable information on inpatient hospital admissions). Linkage of the CPRD and HES datasets for these patients was used to determine hospitalisations and associated costs, as factored into total costs.
The SUEA cohort with HES data included 26 (2.2%) patients <18 years old.
†95% CI, based on 1000 bootstrap replicates.
‡GP visits included consultations with primary care physicians and asthma nurses.
ED, emergency department; GP, general practice; HCRU, healthcare resource use; OCS, oral corticosteroids; SUEA, severe, uncontrolled eosinophilic asthma.
Source: (Kerkhof et al. 2017)

As well as direct costs, severe uncontrolled asthma carries a substantial indirect cost burden due to loss of productivity and absenteeism. Few studies have attempted to quantify this burden, but one UK study found that asthma or asthma symptoms accounted for 2.8 million school absences and 4.1 million lost work days annually, with 36,800 disability living allowance claims (Mukherjee et al. 2016). Another study found that patients who were on maximal dose of ICS/LABA but still uncontrolled had 9-12 additional days of work lost per year (for those aged ≥19) (Sullivan et al. 2007). Further, in a pooled analysis of severe asthma patients with blood eosinophils ≥300 cells/μl and ≥3 exacerbations in the previous year from the SIROCCO and CALIMA benralizumab trials (the subgroup for which a NICE recommendation is sought), a mean estimated average of 6 hours was lost from work per week due to health problems at baseline (AstraZeneca data on file 2017, Xu et al. 2017).

Burden of OCS use

Patients with severe uncontrolled asthma are more likely to need frequent use of OCS compared with patients with moderate disease (ENFUMOSA 2003, Antonicelli et al. 2004, Van et al. 2006, Moore et al. 2007, Heaney et al. 2010); approximately 40% of severe asthma patients regularly use OCS to control their asthma in the UK. Patients with a high blood eosinophil count are also more often OCS-dependent compared with those with low blood eosinophils (20.8% versus 8.9%, respectively)(de Groot et al. 2016).

Frequent or chronic use of OCS in asthma is 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 mellitus (Manson et al. 2009, Lefebvre et al. 2015, Price 2017).

To better understand the impact of OCS use in a UK population, AstraZeneca recently conducted a real-world study using CPRD linked with HES data and OPCRD, which looked at the association between different measures of OCS exposure and the incidence of related conditions, both in the overall patient population and those diagnosed with asthma. The study further evaluated healthcare resource use over time and by dose exposure (AstraZeneca data on file 2017).

[redacted]

[redacted]

[redacted]

A study based on British Thoracic Society Difficult Asthma Registry data (n=596) also demonstrated that maintenance OCS treatment is a significant predictor of cost. Patients on maintenance OCS on average cost 43% more than those not on maintenance OCS. Non-medication costs (19% greater) and non-asthma-related medication were also higher (58% greater) for patients on OCS maintenance therapy. Non-asthma medication included proton pump inhibitors and bisphosphonates, examples of therapies used to manage side effects of OCS-induced morbidity (O'Neill et al. 2015).

Similarly, a study based on CPRD/OPCRD data found that asthma patients who were receiving maintenance OCS compared with patients in the overall asthma population incurred an average each year of:

- 1.7 times more GP visits (1.93 versus 1.36, respectively)
- 5.7 times more hospital-based specialist visits (0.31 versus 0.04, respectively)
- 6.7 times more hospitalisations (0.04 versus 0.01, respectively)
- 2.1 times higher medication costs (£363.6 versus £170.1, respectively), and
- 2.5 times higher overall costs (£552 versus £222, respectively)

in terms of mean asthma-related HCRU and associated direct costs (Kerkhof et al. 2017). These findings are reflective of the higher disease burden faced by patients requiring OCS.

B.1.3.2 Current clinical pathway

Goal of treatment

The aim of asthma management is control of the disease. Complete control of asthma is defined as (BTS/SIGN 2016):

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV_1 and/or PEF>80% predicted or best)
- minimal side effects from medication.

For patients with severe asthma, many of these goals will be inaccessible, and priorities may surround relative rather than complete improvements for these outcomes (NHS England 2017).

General treatment approach

Medications to treat asthma can be described as controllers or relievers.

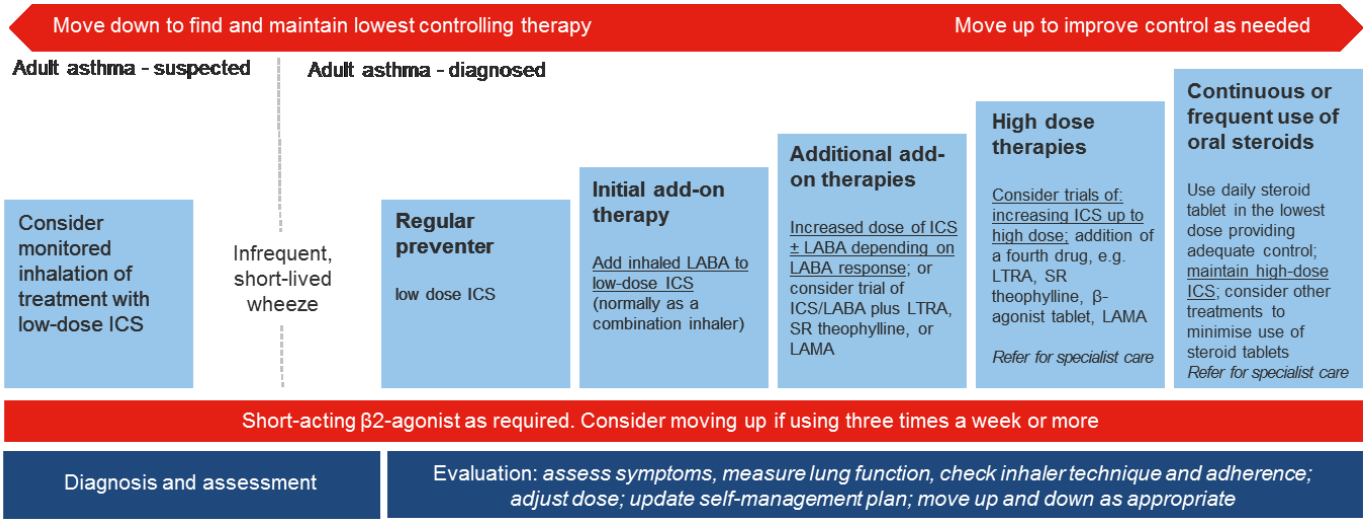
Controllers are maintenance medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. Controllers include inhaled corticosteroids (ICS), ICS/long-acting β-agonist (LABA) combinations, leukotriene modifiers, sustained release theophylline, and long-acting muscarinic antagonists (LAMA) (BTS/SIGN 2016, GINA 2017). Previously, systemic oral corticosteroids (OCS) were the only option for asthmatics not controlled by these therapies; however, for severe allergic asthmatics with recurrent exacerbations, the anti-immunoglobulin E (IgE) monoclonal antibody omalizumab is available, while the IL-5-targeting therapies mepolizumab and reslizumab were both approved by NICE in 2017.

Relievers are used on an as-needed basis to control acute symptoms of asthma by promoting bronchodilation. These medications are usually short-acting oral β_2 agonists (SABAs), but also include options such as inhaled anticholinergics, short-acting theophylline, and ICS/LABAs that have a maintenance and reliever therapy (MART) licence as a reliever.

Treatment guidelines

In the UK, the most commonly used treatment guidelines are those from BTS/SIGN and those recently published by NICE. Key principles of pharmacological management for asthma, as described by BTS/SIGN, are presented in Figure 9 (BTS/SIGN 2016).

Figure 9: BTS/SIGN guidelines for the management of asthma



ICS = inhaled corticosteroid; LABA = long acting beta agonist; LTRA = leukotriene receptor antagonist; LAMA = long acting muscarinic receptor antagonist

Source: (BTS/SIGN 2016)

A stepwise approach to treatment is recommended, moving up to improve control as needed, and moving down to find and maintain the lowest controlling therapy.

ICS are the recommended preventer drug for adults and children, for achieving overall treatment goals. LABAs are the first choice for add-on therapy to ICS in adults, and should be considered before increasing the dose of ICS. If asthma control remains suboptimal after the addition of a LABA, more intense treatment should be considered following a reassessment of diagnosis, adherence, and inhaler technique. For patients who demonstrate an improvement when a LABA is added but for whom control remains inadequate, options include increasing the ICS dose, or adding on a LTRA, LAMA, or theophylline. For patients who do not demonstrate an improvement when a LABA is added, the LABA should be stopped and an increased dose of ICS, an LTRA, or a LAMA (off-label) should be added.

For patients who are inadequately controlled on a combination of SABA, medium-dose ICS, and an additional drug (usually a LABA), there are limited options. BTS/SIGN states that the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit in inadequately controlled adults, although results are currently inconclusive. Other options include stepping up ICS to a high dose (adults) or medium dose (children), or adding an LTRA, theophylline, or slow-release β2 agonist. BTS/SIGN does not indicate a preference for either of these options based on the available evidence, although it is acknowledged that the potential for side effects is greater with theophyllines and β2 agonist tablets.

The recently updated NICE guidance on asthma management also recommends a stepwise approach, but with some differences in the sequence of treatment options (such as earlier positioning of ICS/LTRA, and a preference for a maintenance and reliever regimen over SABA for reliever therapy if uncontrolled on low-dose ICS/LABA) (NICE 2017).

Severe uncontrolled asthma

For those patients who remain inadequately controlled despite stepping up to high dose therapies, the recommended treatment option is daily OCS (prednisolone), at the lowest dose providing adequate control. Patients requiring OCS should generally be referred to specialist care, and monitored for OCS-induced side effects, such as elevated blood pressure, diabetes, decreased bone mineral density (BMD), cataracts, and glaucoma.

Alternatives to OCS are severely limited, but include the biologic treatments mepolizumab and omalizumab (Siergiejko et al. 2011, Bel 2014)(OCS-sparing data for reslizumab have not been published).

Mepolizumab has a marketing authorisation as an add-on treatment for severe refractory eosinophilic asthma in adult patients. Mepolizumab is a humanised, IL-5 antagonist monoclonal antibody that acts by binding to IL-5 and inhibiting IL-5 signalling, thereby reducing the production and survival of eosinophils. Mepolizumab is administered via SC injection, once every 4 weeks. Regulatory approval was granted on the basis of three RCTs – DREAM, MENSA, and SIRIUS, which demonstrated an improvement in exacerbation rates compared with placebo (Pavord 2012, Bel 2014, Ortega et al. 2014). The most commonly-reported side effects in clinical trials were headache, injection-site reactions, back pain (EMA 2016).

NICE has recommended mepolizumab as an add-on to optimised standard therapy, as an option for treating severe refractory eosinophilic asthma in adults, only if: the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months; and, the person has agreed to and followed the optimised standard treatment plan, and has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months; or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months. Continuation of treatment is conditional on an adequate response at 12 months and each year thereafter (NICE 2017).

Reslizumab is licensed as add-on therapy in adult patients with severe eosinophilic asthma, inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment. Reslizumab is administered by IV infusion every 4 weeks; the recommended dose is dependent on body weight. Like mepolizumab, reslizumab is a humanised monoclonal antibody that binds to IL-5, interfering with the activity and survival of eosinophils. Reslizumab was approved based on the results from three pivotal trials that showed improvements in asthma exacerbations compared with placebo (Castro et al. 2011, Castro et al. 2015). Blood creatine phosphokinase increased is listed as the only common AE in the SmPC, with anaphylactic reaction and myalgia listed as uncommon (EMA 2017).

NICE has recommended reslizumab for adult patients with a blood eosinophil count of ≥400 cells per µl, AND who have had three or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months. Continuation of treatment is conditional on an adequate response at 12 months and each year thereafter.

Omalizumab is licensed as add-on therapy to improve control of asthma in adults and children with severe persistent allergic asthma who have: a positive skin test or in vitro reactivity to a perennial aeroallergen; reduced lung function (FEV_1<80% in adults and adolescents); frequent daytime symptoms or night-time awakenings; and multiple documented severe exacerbations despite daily high-dose ICS plus LABA. Omalizumab should only be considered for patients with convincing IgE-mediated asthma. Administration is every 4 weeks by SC injection, with the appropriate dose depending on baseline IgE levels and body weight. Omalizumab works by binding to IgE and preventing it from binding to its receptor on basophils and mast cells, thereby reducing the concentration of free IgE available to trigger the allergic cascade. Regulatory approval was on the basis of one study that demonstrated a reduced rate of asthma exacerbations for omalizumab compared with placebo. The most commonly reported adverse reactions in adults in clinical studies were headache, injection site reactions, and upper abdominal pain (EMA 2016).

NICE has recommended omalizumab as an option for severe persistent confirmed allergic IgE-mediated asthma, as an add-on to optimised standard therapy in people aged ≥6 years who need continuous or frequent treatment with OCS (defined as ≥4 courses in the previous year).

Outside of the UK, the GINA guidelines provide a globally accepted standard that has been adopted by several European countries (GINA 2017). The GINA guidelines are broadly similar to BTS/SIGN, but differences remain regarding dosing categories for ICS use and definitions of exacerbations.

Current treatment patterns in the UK

A 2010 study based on data from the UK severe asthma registry (N=382) reported that 41.7% of refractory asthma patients (based on the American Thoracic Society [ATS] definition) were receiving maintenance OCS, with a mean OCS dose of 15 mg (Heaney et al. 2010). A more recent study based on OPCRD/CPRD data found that 16.6% of patients with severe eosinophilic asthma (SUEA) were receiving maintenance OCS, compared with 2.9% of patients in the overall asthma population; all SUEA patients in this study were also receiving high-dose ICS+LABA, compared with 12.8% in the overall population (Kerkhof et al. 2017). A sub-analysis of data from this study found that 56% of patients who had experienced 3 or more exacerbations in the past year and had an eosinophil count of at least 300 cells/µl were receiving maintenance OCS (AstraZeneca data on file 2017).

In terms of biologic treatments, the NHS innovation scorecard has shown increasing use of mepolizumab and omalizumab since these were recommended by NICE (in 2017 and 2013, respectively), with an estimated 5.2 and 624 defined daily doses used per 100,000 population, respectively, in Q4 2016/17 (defined daily dose is a WHO measure that represents the assumed average maintenance dose per day for a drug used for its main indication in adults) (NHS Digital 2017).

Unmet needs

Despite high-dose ICS plus a second controller (and/or systemic corticosteroids), some severe asthma patients remain uncontrolled, continuing to suffer with daily symptoms, limited lung function, frequent exacerbations, and poor QoL. These patients also often resort to long-term dependence on chronic OCS (Price et al. 2014), which has a significant impact on their lives (Walsh et al. 2001, Dean et al. 2009, Iribarren et al. 2012, Hyland et al. 2015).

Patients with severe uncontrolled asthma and an eosinophilic phenotype present significant clinical, humanistic, health, and cost burdens that demand optimised therapy for driving improved outcomes (Hospers et al. 2000, Garcia et al. 2013, Talini et al. 2015, de Groot et al. 2016, Price et al. 2016).

Existing targeted therapies are limited in many patients with severe eosinophilic asthma. For example, omalizumab, which specifically targets IgE, is not known to be effective in severe non-allergic eosinophilic asthma, and is also poorly effective in severe allergic asthmatics requiring maintenance OCS (Hanania et al. 2011). Biologics that target the cytokine IL-5 (mepolizumab and reslizumab) indirectly target eosinophils, causing a decline in blood eosinophilia, but show only variable efficacy in reducing tissue eosinophilia and no effect on the number of eosinophil progenitors in the bone marrow (NAEPP 2007, Straumann et al. 2010, Fulkerson et al. 2013, Rosenberg et al. 2013, Mukherjee et al. 2014). Mepolizumab also requires reconstitution before subcutaneous administration, while reslizumab requires an intravenous infusion. Both require 4-weekly dosing (reslizumab dosing is also weight-dependent), with associated resource use.

New, targeted products are therefore needed to reduce the frequency and severity of exacerbations and hospitalisations, avoid further loss of pulmonary function, and limit drug toxicity associated with OCS, while providing dosing simplicity and convenience for patients.

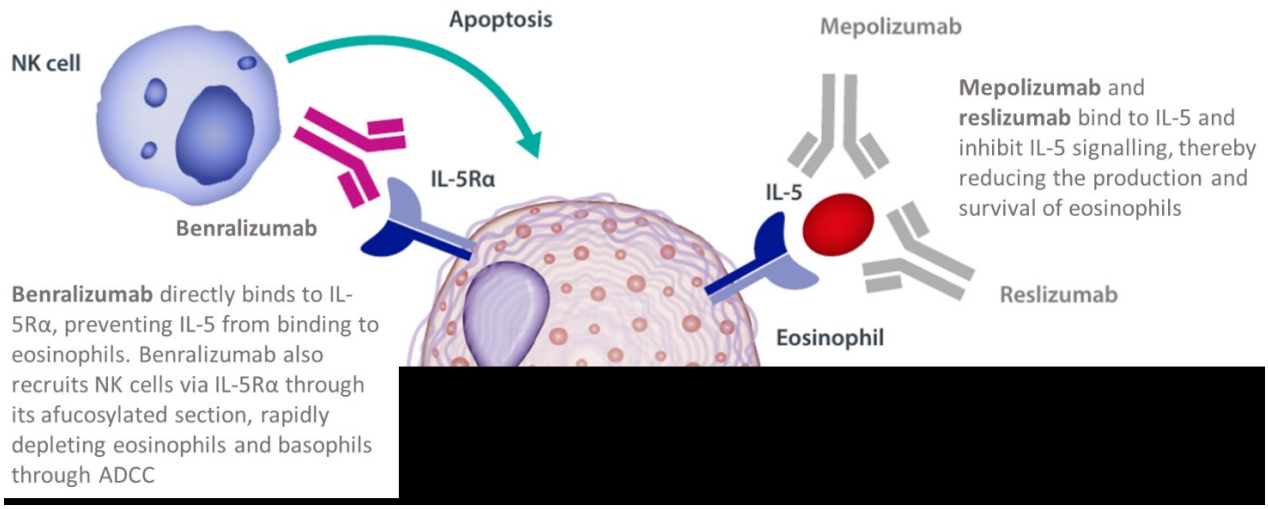
Role of benralizumab in the clinical pathway

Benralizumab is expected to meet unmet clinical needs in the treatment of severe, uncontrolled eosinophilic asthma, through its innovative mechanism of action and simple SC dosing schedule.

As an anti-eosinophil humanised, monoclonal antibody, benralizumab specifically binds to the human IL-5 receptor alpha (IL-5Rα), with a unique mode of action. By binding to eosinophils through IL-5Rα, benralizumab blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil. Additionally, due to an afucosylated section on the molecule itself, benralizumab increases the affinity of eosinophils to Natural Killer (NK) cells. This leads to a rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in a systemic efficacy response (Laviolette et al. 2013). Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84 (Laviolette et al. 2013).

In contrast, mepolizumab and reslizumab act by binding to IL-5 and inhibiting IL-5 signalling, thereby indirectly reducing the activation, proliferation, and survival of eosinophils (Figure 1) – this ultimately results in eosinophil reduction but not depletion.

Figure 10: Mode of action of benralizumab

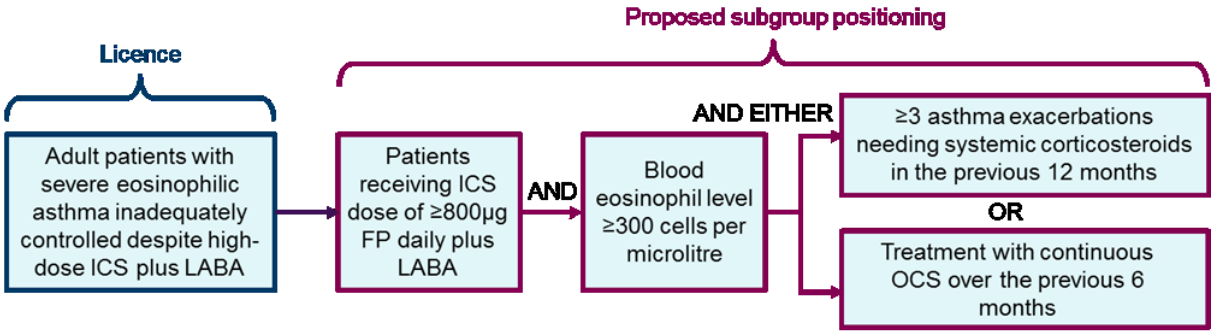


ADCC: Antibody-dependent cell-mediated cytotoxicity; IL-5: Interleukin 5; IL-5R: Interleukin 5 receptor; NK: Natural killer

Currently, benralizumab is also the only anti-eosinophilic treatment available with simple administration via an accessorised prefilled syringe by a healthcare provider for SC injection and every 8-week dosing. The less frequent dosing schedule for benralizumab and avoidance of the need for reconstitution (as for mepolizumab and reslizumab, which also require every 4-weekly dosing) may therefore reduce the humanistic and economic burden of severe asthma through lower resource use.

By targeting the subgroup of patients with ≥300 eosinophils per µl, and either ≥3 prior exacerbations in the past year or 6 months of continuous OCS use (Figure 11), benralizumab can benefit the patients who need it most.

Figure 11: Context of benralizumab in the clinical pathway of care



B.1.4 Equality considerations

AstraZeneca does not anticipate the use of this technology to result in any equality issues.

B.2 Clinical effectiveness

Summary of key points

Overview of clinical trial programme

- The clinical evidence presented in this submission for benralizumab is based on three randomised controlled Phase III trials: SIROCCO, CALIMA, and ZONDA
- The primary outcome in SIROCCO and CALIMA was the reduction in the annual asthma exacerbation rate versus placebo. The primary outcome in ZONDA was the reduction in median daily OCS dose. All three studies were conducted in patients with uncontrolled severe eosinophilic asthma
- The clinical evidence demonstrates that benralizumab is effective at reducing asthma exacerbations, reducing the use of OCS, and improving asthma symptoms. These efficacy outcomes are highly clinically relevant for patients with severe uncontrolled eosinophilic asthma

ITT data versus SOC

In SIROCCO, CALIMA, and ZONDA trials, benralizumab significantly:

- reduced the annual rate of asthma exacerbations by 51% compared with placebo in SIROCCO ($p<0.0001$), by 28% in CALIMA ($p=0.0188$), and by 70% in ZONDA (nominal $p<0.001$) (differences in exacerbation reductions between SIROCCO and CALIMA are likely to have been driven by regional differences in baseline exacerbation history, as well as a strong placebo response in CALIMA)
- reduced a patient's exposure to and dependence on chronic OCS; in ZONDA, benralizumab was associated with a 75% median reduction in OCS dose compared with 25% for placebo ($p<0.001$), and a 4-times higher odds of achieving a reduction in OCS dose. Benralizumab resulted in OCS being completely withdrawn in 52% of eligible patients (vs 19% in placebo; $p=0.002$), thereby reducing and avoiding the long-term detrimental effects of the OCS burden
- improved pulmonary function by 159 ml in SIROCCO ($p=0.0006$), by 116 ml in CALIMA ($p=0.010$), and by 112 ml in ZONDA (NSS; nominal $p=0.129$), compared with placebo, which is clinically meaningful
- reduced asthma symptoms, improved asthma control, and improved asthma-associated QoL, with statistically significant improvements seen for PRO measures including the total asthma symptom score

The rate of adverse reactions (including any AE, AEs leading to discontinuation, and SAEs) across the Phase 3 trials was comparable between the benralizumab and placebo arms. Most AEs were mild to moderate in intensity, and were not considered to be related to treatment.

Sub-group data versus SOC for the population in which a recommendation is sought (severe eosinophilic asthma inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months)

Pooled SIROCCO/CALIMA data (sub-group with high-dose ICS [≥ 800µg FP daily] plus LABA, blood eosinophils ≥ 300 cells/µl, and 3+ exacerbations in prior year): Benralizumab reduced the annual asthma exacerbation rate by 53% (RR: 0.47; 95% CI: 0.32, 0.67; p<0.001), improved FEV_1 by 254 ml (change from baseline of 0.485 vs 0.231, respectively; p<0.001), and improved the ACQ-6 score from baseline by -0.43 points (-1.59 vs -1.16, respectively; p=0.002), compared with placebo when added to SOC.

In the ZONDA subgroup with blood eosinophils ≥300 cells/µl, benralizumab reduced the annual exacerbation rate by [redacted], and the median percentage reduction in OCS dose was [redacted] (Hodges-Lehman difference in medians: [redacted].

Comparative effectiveness versus mepolizumab and reslizumab

In the absence of head-to-head trials against the comparators mepolizumab and reslizumab, the feasibility of conducting an indirect comparison was assessed. Cross-trial differences required a matching-adjusted indirect comparison (MAIC) versus mepolizumab, which showed [redacted]

Analyses were carried out in the overall population, and assumed to be generalisable to the mepolizumab NICE-recommended population, due to a lack of data for mepolizumab in this subgroup. For the comparison between benralizumab and reslizumab, high heterogeneity between trials meant that a robust MAIC was not feasible. Therefore, equivalent efficacy has been assumed for benralizumab and reslizumab in exacerbation reductions and ACQ transitions (reslizumab OCS-sparing data are currently not available).

B.2.1 Identification and selection of relevant studies

Search strategy

A systematic literature review was conducted to identify relevant studies of benralizumab in severe asthma, in accordance with NICE guidance, and the University of York Centre for Reviews and Dissemination (CRD) standards and Cochrane standards. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Searches were conducted on 17th October 2017 in Medical Literature Analysis and Retrieval System Online (MEDLINE®), Excerpta Medica Database (Embase®), MEDLINE® In-Process, and Cochrane (Central Register of Controlled Trials [CENTRAL]) databases. In addition, relevant conference proceedings, manufacturers' websites, and HTA submission dossiers were hand-searched to identify additional relevant evidence.

The search terms included disease terms, a study design filter, and drug terms for agents licensed for the treatment of severe asthma. The study design filter was adapted from the Scottish Intercollegiate Guidelines Network (SIGN) guidelines to identify RCTs using a combination of Medical Subject Headings (MeSH) and free text terms.

A two-stage screening process was adopted, with a first-pass screening for titles and abstracts followed by second-pass screening for full-text publications. Screening was carried out by two independent reviewers, with any discrepancies reconciled by a third independent reviewer.

Study selection

Eligibility criteria were specified in terms of population, intervention, comparators, outcomes and study design (PICOS) criteria, as described in Table 9.

Table 9: Eligibility criteria (PICOs) for the systematic review

Population	• Age: adults and adolescents (≥12 years) • Gender: any • Race: any • Disease: severe asthma that is uncontrolled despite treatment with medium- to high-dose ICS plus at least one additional controller
Interventions	• Benralizumab
Comparators	• Biologics (approved and in development) • Mepolizumab • Omalizumab • Reslizumab • Placebo/best supportive care • Medium or high-dose ICS + at least one additional controller. • Medium dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline)

	• High-dose ICS + 2 additional controller (e.g. LABA + LAMA/LABA+LTRA) • High-dose ICS + at least one additional controller + OCS maintenance treatment	
Outcomes of interest	Efficacy and quality of life outcomes: • Pre-bronchodilator FEV_1 • Post-bronchodilator FEV_1 • Peak expiratory flow • Asthma exacerbation (overall exacerbation, exacerbations requiring systemic corticosteroids, ER visit and/or hospitalisation) • Definition of exacerbation • Number of patients with exacerbations • Total number of exacerbations experienced over the duration of the study • Mean rate of exacerbations per patient per year • Time to first exacerbation • Symptom-free days • Asthma control measured by ACQ • Asthma symptoms (overall, day-time, night-time symptom, night-time awakening) • Oral corticosteroids sparing efficacy • AQLQ or mini AQLQ • SGRQ • EQ-5D • WPAI	
	Safety outcomes: • Any adverse events • Any serious adverse events • Any treatment-related adverse events • Bronchitis • Cardiac events • Cough • Dry mouth	• Hoarseness or dysphonia • Mortality • Nausea • Oral candidiasis • Pneumonia • Palpitations • Sinusitis • Tremor • Upper respiratory tract infections
	Tolerability • All withdrawals • Withdrawal due to adverse events • Withdrawal due to lack of efficacy	
Study designs	• RCTs	
Language	• Database to be searched irrespective of language • English language studies were included in SLR	
Publication timeframe	• Database inception to present date (searched initially on 17th June 2016 and subsequently on 17 October 2017) • Conference proceedings for past 3 years (searched on 17 October 2017)	

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ER: Emergency room; EQ-5D: EuroQoL 5D; FEV_1: Forced expiratory volume in one second; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2 agonist; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene receptor antagonist; RCT: Randomised controlled trial; SGRQ: St. George's Respiratory Questionnaire; SLR: Systematic literature review; WPAI: Work Productivity and Activity Impairment

Identified trials

A total of seven completed clinical studies that met the inclusion criteria were identified for benralizumab (Table 10).

Table 10: Summary of identified benralizumab clinical trials in patients with severe asthma

Study name	Study phase	Sample size (N)	Interventions	Description
SIROCCO (NCT01928771) (Bleecker 2016)	Phase III	1,205	Benralizumab; 30 mg Q4W	Efficacy and safety study of benralizumab added to high-dose ICS plus LABA in patients with uncontrolled asthma
			Benralizumab; 30 mg Q8W	
			Placebo	
CALIMA (NCT01914757) (FitzGerald 2016)	Phase III	1,306	Benralizumab; 30 mg Q4W	Efficacy and safety study of benralizumab added to medium-dose or high-dose ICS plus LABA in patients with uncontrolled asthma
			Benralizumab; 30 mg Q8W	
			Placebo	
ZONDA (NCT02075255) (Nair et al. 2017)	Phase III	220	Benralizumab; 30 mg Q4W	Reducing OCS use in patients with uncontrolled asthma on high dose ICS plus LABA and chronic OCS therapy
			Benralizumab; 30 mg Q8W	
			Placebo	
Castro 2014 (NCT01238861) (Castro et al. 2014)	Phase II	609	Benralizumab; 2 mg	Efficacy study of multiple subcutaneous doses of benralizumab or placebo in adult subjects with uncontrolled asthma
			Benralizumab; 20 mg	
			Benralizumab; 100 mg	
			Placebo	
Park 2016 (NCT01412736) (Park et al. 2016)	Phase II	106	Benralizumab; 2 mg	Efficacy study of the effect of multiple subcutaneous doses of benralizumab on the annual asthma exacerbation rate in adult subjects with uncontrolled, suspected eosinophilic asthma
			Benralizumab; 20 mg	
			Benralizumab; 100 mg	
			Placebo	
Nowak 2015 (NCT00768079) (Nowak et al. 2015)	Phase II	110	Benralizumab 0.3 mg/kg	Efficacy study of single intravenous doses of benralizumab in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation
			Benralizumab 1 mg/kg	
			Placebo	
NCT01947946	Phase II	13	Benralizumab; 30 mg Q4W	Efficacy and safety study of benralizumab added to medium-dose ICS plus LABA in patients with uncontrolled asthma – this trial was terminated due to sponsor decision
			Benralizumab; 30 mg Q8W	
			Placebo	

Of note are two additional key trials for benralizumab (BISE and GREGALE) that did not meet the inclusion criteria. BISE was a randomised, placebo-controlled, double-blind Phase 3 trial in patients with mild to moderate persistent asthma (Ferguson et al. 2017), and was excluded due to being conducted in a milder asthmatic population. GREGALE was a Phase 3 trials that assessed the functionality, reliability, and performance of a pre-filled syringe with benralizumab administered at home, and was excluded as it was open-label and single-arm; further, the trial was not powered to assess efficacy outcomes (Clinicaltrials.gov 2017).

See Appendix D.1 for full details of the process and methods used to identify and select the clinical evidence relevant to this submission.

B.2.2 List of relevant clinical effectiveness evidence

After consideration of the available evidence, three pivotal Phase 3 randomised, controlled studies were considered the most relevant to the decision problem, i.e., patients with severe, uncontrolled eosinophilic asthma: SIROCCO, CALIMA, and ZONDA (Table 11).

- SIROCCO and CALIMA were similar studies that evaluated the efficacy and safety of benralizumab in patients with asthma who remained uncontrolled on high (SIROCCO) or medium to high (CALIMA) doses of ICS/LABA, with or without concomitant OCS
- ZONDA was an OCS sparing trial, that aimed to confirm if benralizumab can reduce OCS dependence (after dose optimisation) in patients who are uncontrolled on high-dose ICS plus LABA, and chronically dependent on OCS

Two different dosing regimens were evaluated in the above Phase 3 trials. In line with the licensed indication, only the results for the licensed dose (Q8W) will be presented. While the full ITT results are presented here, to reiterate, the focus of this submission is on the patient subgroup for which a NICE recommendation is sought (i.e., patients with blood eosinophil count ≥300 cells per µL, and either ≥3 exacerbations needing systemic corticosteroids in the past 12 months, or ≥6 months previous treatment with OCS), with subgroup analyses from SIROCCO, CALIMA, and ZONDA demonstrating the safety and efficacy of benralizumab in this specific patient group.

In terms of identified but excluded studies, Castro 2014, Nowak 2015, and Park 2016 were excluded because they were Phase 2 studies that evaluated unlicensed dosing regimens of benralizumab. Study NCT01947946 was excluded as it was terminated with 13 randomised patients and no results were available.

Table 11: Clinical effectiveness evidence

Study	SIROCCO (NCT01928771) (Bleecker 2016)			CALIMA (NCT01914757) (FitzGerald 2016)	ZONDA (NCT02075255) (Nair et al. 2017)
Study design	Randomised, Double-blind, Parallel Group, Placebo controlled			Randomised, Double-blind, Parallel Group, Placebo controlled	Randomised, Double-blind, Parallel Group, Placebo controlled
Population	12 to 75 years with uncontrolled asthma receiving high-dose ICS plus LABA with/without additional asthma controller(s) and having a history of 2 or more asthma exacerbations in prior year (N=1,204 randomised and received treatment, pre-specified blood eosinophil ≥300/μL and <300/μL [2:1])			12 to 75 years with uncontrolled asthma receiving medium to high-dose ICS plus LABA with/without additional asthma controller(s) and having a history of 2 or more asthma exacerbations in the prior year (N=1306 randomised and received treatment, pre-specified blood eosinophil ≥300/μL and <300/μL [2:1])	18-75 years with uncontrolled asthma receiving high-dose ICS plus LABA and chronic OCS with or without additional asthma controller(s) with blood eosinophils ≥150 cells/μL and having a history of 1 or more exacerbation in the prior year
Intervention(s)	For adults and non-EU adolescents: 30 mg subcutaneous injection for 48 weeks of either: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 4 (with placebo injection at the 4W interim) For EU adolescents:* 30 mg subcutaneous injection for 48 weeks treatment period of: • Benralizumab Q4W x 3 and Q8W x 4			For adults and non-EU adolescents: 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) For EU adolescents:* 30 mg subcutaneous injection for 56 weeks treatment period of: • Benralizumab Q4W x 3 and Q8W x 5	30 mg subcutaneous injection for 28 weeks treatment period of either: • Benralizumab Q4W • Benralizumab Q4W x 3 and Q8W x 2 (with placebo injection in interim)
Comparator(s)	For adults and non-EU adolescents: Placebo Q4W For EU adolescents: Placebo Q4W x 3 and Q8W x 4			For adults and non-EU adolescents: Placebo Q4W For EU adolescents: Placebo Q4W x 3 and Q8W x 5	Placebo Q4W
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes	Yes to both	Yes to both

Rationale for use/ non-use in the model	Pivotal clinical trial	Pivotal clinical trial	Pivotal clinical trial
Reported outcomes specified in the decision problem	• Annual asthma exacerbation rate (primary endpoint) • Pulmonary function • Asthma symptom score and other asthma control metrics (e.g., ACQ-6) • Exacerbations associated with emergency room visit or hospitalisation • QoL (AQLQ(S)+12, EQ-5D) • HCRU and productivity loss (WPAI+CIQ)	• Annual asthma exacerbation rate (primary endpoint) • Pulmonary function • Asthma symptom score and other asthma control metrics (e.g., ACQ-6) • Exacerbations associated with emergency room visit or hospitalisation • QoL (AQLQ(S)+12, EQ-5D) • HCRU and productivity loss (WPAI+CIQ)	• Percentage reduction in final OCS dose compared with baseline (primary endpoint) • Proportion of patients with 25%, 50% and 100% reduction, and final OCS dose ≤5.0 mg/day • Annual asthma exacerbation rate • Exacerbations associated with emergency room visit or hospitalisation • Pulmonary function • Asthma symptom score and other asthma control metrics (e.g., ACQ-6) • QoL (AQLQ(S)+12)
All other reported outcomes	N/A	N/A	N/A

* The rationale for the different dosing regimen in adolescents in the EU was based on the Paediatric Committee at the European Medicines Agency's (PDCO) request to limit drug burden in adolescents and to study only the less frequent dose in this patient population

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

The methodology for the three key trials is summarised in Table 12, and is presented in further detail below.

Table 12: Comparative summary of trial methodology

Trial	SIROCCO (NCT01928771)	CALIMA (NCT01914757)	ZONDA (NCT02075255)
Trial design	Randomised, Double-blind, Parallel Group, Placebo controlled	Randomised, Double-blind, Parallel Group, Placebo controlled	Randomised, Double-blind, Parallel Group, Placebo controlled
Key eligibility criteria for participants*	• Aged 12–75 years • Weight at least 40 kg • 2 or more asthma exacerbations in prior year • Uncontrolled asthma receiving high-dose ICS plus LABA with/without additional asthma controller(s)	• Aged 12–75 years • Weight at least 40 kg • 2 or more asthma exacerbations in prior year • Uncontrolled asthma receiving medium to high-dose ICS plus LABA with/without additional asthma controller(s)	• Aged 18-75 years • Receiving high-dose ICS plus LABA and chronic OCS with or without additional asthma controller(s) • Blood eosinophils ≥150 cells/μL • 1 or more asthma exacerbations in prior year
Settings and locations where the data were collected	374 centres in 17 countries, including 24 UK centres	303 centres in 11 countries	89 centres in 12 countries
Trial drugs	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo^	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo^	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo
Permitted and disallowed concomitant medication	Patients continued to receive any other asthma-controller medications	Patients continued to receive any other asthma-controller medications	Patients continued to receive any other asthma-controller medications
Primary outcomes	Annual asthma exacerbation rate ratio versus placebo	Annual asthma exacerbation rate ratio versus placebo	Percentage reduction in oral glucocorticoid dose from baseline to week 28

Other outcomes used in the economic model/specified in the scope	Prebronchodilator FEV_1, total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48, time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events	Prebronchodilator FEV_1, total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 56, time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events	% of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase, and the % of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained. Annual asthma exacerbation rate, time to the first asthma exacerbation, percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalisation), FEV_1 before bronchodilation, total asthma symptom score, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events
Pre-planned subgroups	• Baseline OCS use • Sex • Age • Geographic region • Body mass index • Number of exacerbations in the previous year • Race • Nasal polyps at baseline • Immunoglobulin E at baseline • Atopic asthma at baseline • Prior treatment with omalizumab • Blood eosinophil levels	• Baseline OCS use • Sex • Age • Geographic region • Body mass index • Number of exacerbations in the previous year • Race • Nasal polyps at baseline • Immunoglobulin E at baseline • Atopic asthma at baseline • Prior treatment with omalizumab • Blood eosinophil levels	• Age • Gender • Body mass index • Number of exacerbations in the previous year • Geographical region • OCS dose at baseline • Blood eosinophil levels

* Medium dose defined as >250µg FP equivalent per day and high dose as >500µg for adults

^ EU adolescents in SIROCCO and CALIMA received benralizumab Q4W for the first three doses and Q8W thereafter, or matching placebo at these intervals. The rationale for the different dosing regimen in adolescents in the EU was based on the Paediatric Committee at the European Medicines Agency's (PDCO) request to limit drug burden in adolescents and to study only the less frequent dose in this patient population

Trial design

SIROCCO and CALIMA

The two similarly designed primary registration studies, SIROCCO and CALIMA, evaluated patients 12 years to 75 years of age with uncontrolled asthma and a history of exacerbations, still symptomatic despite using medium-to-high-dose (CALIMA) or high-dose (SIROCCO) ICS plus LABA with or without OCS or additional controller medications (GINA Steps 4 and 5/NAEPP Steps 5 and 6) (NAEPP (NAEPP 2007, GINA 2017). There were 2 benralizumab dosing regimens: every 4 weeks [Q4W] and every 8 weeks [Q8W]).

The primary endpoint in each study was the annual rate of asthma-related exacerbations, with key secondary endpoints being FEV_1 and asthma symptoms as defined by a daily patient diary. Other secondary endpoints included asthma symptom score and other asthma control metrics (e.g., ACQ-6, QoL (AQLQ(S)+12, EQ-5D), HCRU, and productivity loss (WPAI+CIQ). A pooled analysis was pre-specified for SIROCCO and CALIMA to better understand the relationship between the clinical efficacy of benralizumab, and blood eosinophil count and exacerbation history (FitzGerald et al. 2017). Study endpoints were evaluated over a 48-week treatment period in SIROCCO and a 56-week treatment period in CALIMA.

Randomised patients were stratified by baseline blood eosinophil counts ≥300 cells/μL and <300 cells/μL at a ratio of 2:1. Both studies were prospectively powered for the primary efficacy analysis of annual rate of asthma-related exacerbations in the stratum of patients on high-dose ICS plus LABA with blood eosinophils ≥300/μL. This stratification approach allows for the effect of benralizumab on the primary and the 2 key secondary endpoints to be characterised across the full range of baseline blood eosinophil counts, although all multiplicity-protected analyses in both studies were in the primary population of patients on high-dose ICS plus LABA with blood eosinophils ≥300 cells/μL. The cut-off of 300 cells/μl was consistent with the approach in Phase 2b benralizumab trials (Castro et al. 2014) as well as mepolizumab studies, which showed this level to be a useful predictive biomarker of response to anti-IL5 therapies. Additional cut-offs at eosinophil thresholds of 0, 150, and 450 cells/μl were also explored and are presented for the pooled analysis (FitzGerald et al. 2017).

In the CALIMA trial, 16% patients (n=215) on medium-dosage ICS plus LABA (defined as 500 μg/day fluticasone equivalent) were not included in the regulatory filing. All analyses included in this submission are conducted on patients on high dose ICS/LABA defined as ICS daily dose >500 μg fluticasone equivalent per the GINA guideline (GINA 2017); results for patients on medium-dose ICS/LABA are not presented. (All adult patients in SIROCCO received high-dose ICS plus LABA; adolescents received medium or high-dose ICS [≥500 μg] plus LABA.)

Pre-planned subgroup analyses were carried out for the following patients in SIROCCO and CALIMA in patients with eosinophils ≥300 cells/µl:

- Baseline OCS use (yes/no)
- Sex (male/female)
- Age (<18, 18–<65, or ≥65 years)
- Geographic region (Asia, Eastern Europe, Europe [excluding Eastern Europe], North America, or South America)
- Body mass index (≤35/>35 kg/m^2)
- Number of exacerbations in the previous year (2, 3, or ≥4).
- Race (white, black or African-American, Asian, or other).
- Nasal polyps at baseline (yes/no)
- Immunoglobulin E at baseline (≤30, >30–≤700, or >700 IU/L)
- Atopic asthma at baseline (yes/no)
- Prior treatment with omalizumab (yes/no)

In addition, analyses for baseline blood eosinophil count categories (<150/µL, 150-299/µL, 300-449/µL, ≥450/ µL) were prespecified.

ZONDA evaluated patients 18 years to 75 years of age with severe asthma who required treatment with high-dose ICS plus LABAs and chronic OCS therapy with or without additional controller medications. The same 2 dosing regimens (Q4W and Q8W) studied in SIROCCO and CALIMA were also studied in ZONDA, and compared with placebo, over a 28-week treatment period. Following enrolment, patients entered a run-in phase that included stabilisation of the OCS dose (reduced until the minimum effective dose without loss of asthma control was reached), prior to the randomised intervention period.

The primary endpoint in this study was the percentage reduction in final OCS dose compared with baseline, while maintaining asthma control. In this study, eligible patients with a peripheral blood eosinophil count of ≥150/µL were randomised. Secondary endpoints included the proportion of patients with ≥50% and 100% reduction in average daily OCS dose while maintaining asthma control; the proportion of patients with an average final OCS dose ≤5.0 mg daily while maintaining asthma control; annual asthma exacerbation rate and other exacerbation parameters; pre-bronchodilator FEV_1; asthma symptoms; ACQ-6 score; and AQLQ(S)+12 score.

Pre-planned subgroup analyses were conducted for the following patients:

- Age (≥18 to <65 and ≥65 years)
- Gender (male/female)

- BMI (≤35 kg/m2, >35 kg/m^2)
- Number of exacerbations in the previous year (1, 2, or ≥3)
- Region (Asia, Central and Eastern Europe, Western Europe and Turkey, European Union, North America, and RoW)
- OCS dose at baseline (≤10 mg, >10 mg)
- Blood eosinophils ≥300 cells/µl

Eligibility criteria

SIROCCO, CALIMA, and ZONDA enrolled patients whose asthma was uncontrolled on ICS/LABA therapy. A summary of the key eligibility criteria is presented below, with a full list of key inclusion and exclusion criteria presented in Appendix D.1.

SIROCCO

Patients aged 12–75 years who weighed at least 40 kg, with physician-diagnosed asthma needing treatment with medium to high-dosage ICS plus LABA for at least 12 months before enrolment and with high-dose ICS plus LABA for at least 3 months before enrolment (week –4) were included in SIROCCO. Patients were required to have had at least two documented asthma exacerbations needing systemic corticosteroid treatment or a temporary increase in their usual maintenance dosages of OCS within 1 year before enrolment. Patients must have also had documented treatment of ICS plus LABA with or without OCS and additional asthma controllers for at least 3 months before enrolment. Patients aged 18 years or older were permitted only high-dosage ICS treatment, whereas patients aged 12–17 years could have been receiving medium-dosage or high-dosage ICS. Additional inclusion criteria included a prebronchodilator FEV1 <80% predicted (<90% predicted for patients aged 12–17 years) at screening (week –3); a documented post-bronchodilator reversibility of at least 12% and at least 200 mL in FEV1 within 12 months before enrolment or identified at screening; and an ACQ-6 score of at least 1.5 at enrolment.

Patients were excluded from the study if they had a history of anaphylaxis with any biologic drug, a clinically important pulmonary disease other than asthma, or a helminthic parasitic infection diagnosed within 24 weeks before enrolment that had either not been treated or did not respond to standard-of-care treatment.

CALIMA

The eligibility criteria in CALIMA were the same as those in SIROCCO, with the key difference of ICS dose: adult patients in SIROCCO were required to be receiving high-dose ICS whereas adult patients in CALIMA could be receiving medium-dose ICS or high-dose ICS (medium dose defined as 500 µg; high dose defined as >500 µg fluticasone dry powder formulation or equivalent).

ZONDA

Adult patients were eligible to participate in ZONDA if they had a blood eosinophil count of 150 cells or more per cubic millimetre and had asthma that had been treated with medium-dose to high-dose ICS and LABA therapy for at least 12 months before enrolment, and with high-dose ICS and LABA therapy for at least 6 months before enrolment. Patients were required to have been receiving OCS therapy for at least 6 continuous months directly before enrolment (equivalent to a prednisolone or prednisone dose of 7.5 to 40.0 mg per day).

Settings and locations where the data were collected

SIROCCO

Patients were enrolled at 374 centres in 17 countries (Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russian Federation, South Africa, South Korea, Spain, Turkey, United Kingdom, USA, and Vietnam), including 24 UK centres.

CALIMA

Patients were enrolled at 303 centres in 11 countries (Argentina, Canada, Chile, Germany, Japan, Philippines, Poland, Romania, Sweden, Ukraine, and USA).

ZONDA

Patients were screened at 89 centres, and received treatment at 64 centres, in 12 countries (Argentina, Bulgaria, Canada, Chile, France, Germany, Poland, South Korea, Spain, Turkey, Ukraine, and USA).

Trial drugs and concomitant medications

Trial drugs

In SIROCCO, CALIMA, and ZONDA, benralizumab was administered as a 30 mg/mL solution for injection in accessorised pre-filled syringe, 1mL fill volume. Benralizumab was administered subcutaneously every 4 weeks (Q4W), or every 4 weeks for the first three doses and every 8 weeks thereafter (Q8W) (with matching placebo at the 4-week interim to maintain blinding). Matching placebo was administered every 4 weeks to those randomised to the control arm.

For EU adolescents in SIROCCO and CALIMA only, benralizumab was administered Q4W for the first 3 doses and Q8W thereafter, with matching placebo at these intervals in the control arm. The rationale for the different dosing regimen in adolescents in the EU was based on the Paediatric Committee at the European Medicines Agency's (PDCO) request to limit drug burden in adolescents and to study only the less frequent dose in this patient population.

As discussed above, this submission focuses on the Q8W dose, in line with the marketing authorisation.

Concomitant medications

All patients were required to be treated with ICS and LABA for at least 3 months prior to Visit 1 and during the course of each study. Patients continued to receive any asthma-controller medications (including leukotriene modifiers, long-acting muscarinic antagonists, OCS, and theophylline), throughout the study. Short-acting β2-agonists were permitted as rescue medications. Changes to the patient's background controller regimen were discouraged during the treatment period, unless judged medically necessary by the investigator.

Outcomes

Primary outcome

In SIROCCO and CALIMA, the primary efficacy endpoint was the annual asthma exacerbation rate ratio versus placebo, which is summarised as total number of exacerbations x 365.25/total duration of follow-up within the treatment group (days). An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) emergency department or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥24 h) because of asthma. Worsening of asthma was defined as any new or increased symptoms or signs that were concerning to the patient or related to an Asthma Daily Diary alert. The primary and key secondary analyses of efficacy included patients with blood eosinophil counts at least 300 cells per µL. (All efficacy endpoints were also assessed in patients with blood eosinophil counts less than 300 cells per µL, but statistical comparisons were not done for patients with less than 300 eosinophils per µL for non-key secondary outcomes (except for ACQ-6).)

In ZONDA, the primary endpoint was the percentage reduction in the OCS dose from baseline (randomisation at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained. Results were stratified by baseline eosinophil level (≥150 to <300 cells per µL vs. ≥300 cells per µL).

Secondary outcomes

In SIROCCO and CALIMA, key secondary endpoints were prebronchodilator FEV_1 and total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48 (SIROCCO) or week 56 (CALIMA). Additional secondary endpoints were time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, HRU, CGIC, and PGIC.

In ZONDA, secondary endpoints included the percentages of patients who had a reduction in the average daily OCS dose of 25% or more, of 50% or more, or of 100% (discontinuation of OCS therapy) from baseline to end of the maintenance phase, and the percentage of patients with an average final OCS dose of 5.0 mg or less per day while asthma control was maintained. Additional end points included the annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalisation), the FEV_1 before bronchodilation, the total asthma symptom score, the ACQ-6 score, the EQ-5D score, and the AQLQ(S)+12 score. Exploratory end points were used to investigate the effect of blood and sputum eosinophilia on the efficacy of the trial drug.

In all three trials, safety outcomes including rates of AEs, serious AEs, AEs leading to discontinuation, laboratory variables, ECGs, vital signs, immunogenicity, and deaths were also reported.

Patient characteristics

SIROCCO

A total of 1204 patients received at least one dose of treatment in the SIROCCO trial. Baseline characteristics were similar between treatment arms, as well as between patients with blood eosinophil counts at least 300 cells per µL and less than 300 cells per µL (Table 13). Use of maintenance asthma treatment use was similar across groups, with a mean fluticasone propionate or equivalent total daily dosage of 899 µg (range 125–3000). Overall, 196 (16%) patients were receiving oral corticosteroids, with similar dosing between cohorts.

Table 13: Baseline patient characteristics in the SIROCCO trial

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)
Age (years)	48.7 (14.9)	50.1 (13.4)	47.6 (14.5)	48.6 (14.7)	49.2 (13.1)	47.6 (14.6)
Sex						
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)
Race						
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)
Hispanic or Latino ethnicity	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)
BMI (kg/m^2)	28.9 (7.1)	29.2 (7.1)	28.2 (6.2)	28.7 (7.0)	28.9 (6.9)	27.7 (6.1)
Eosinophil count (cells per µL)	370 (0–2690)	390 (0–3440)	360 (0–3100)	500 (300–2690)	500 (300–3440)	500 (300–3100)
Central eosinophil count (cells per µL)	350 (0–3580)	360 (0–3170)	325 (0–3110)	480 (70–2220)	470 (40–3170)	460 (10–3110)
Prebronchodilator FEV_1 (L)	1.660 (0.584)	1.655 (0.553)	1.680 (0.582)	1.654 (0.580)	1.673 (0.577)	1.660 (0.574)
Predicted normal	56.6% (15.0)	57.4% (14.1)	56.1% (14.6)	56.4% (14.6)	56.5% (14.4)	55.5% (14.6)
Prebronchodilator FEV_1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)
Reversibility	20% (−26 to 154)	18% (−7 to 136)	22% (−12 to 157)	20% (−26 to 154)	18% (−7 to 136)	21% (−10 to 157)
ACQ-6 score†	2.87 (0.94)	2.77 (0.96)	2.80 (0.88)	2.90 (0.95)	2.77 (0.95)	2.81 (0.89)
Time since asthma diagnosis (years)	14.2 (1.1–72.4)	15.3 (1.1–70.4)	14.4 (1.1–66.9)	13.4 (1.1–65.2)	14.9 (1.1–62.6)	14.6 (1.1–66.9)

Number exacerbations in past 12 months	3.0 (1.8)	2.9 (1.8)	2.8 (1.5)	3.1 (2.0)	3.0 (2.0)	2.8 (1.5)
2 (%)	244 (60.0)	253 (63.4)	252 (63.3)	149 (55.8)	173 (62.9)	164 (61.4)
3 (%)	76 (18.7)	64 (16.0)	79 (19.8)	53 (19.9)	44 (16.0)	53 (19.9)
≥4 (%)	87 (21.4)	82 (20.6)	67 (16.8)	65 (24.3)	58 (21.1)	50 (18.7)
Number resulting in ED visit	0.3 (0.8)	0.3 (1.0)	0.2 (0.8)	0.3 (0.8)	0.4 (1.0)	0.3 (0.9)
Patients with ≥1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)
Number resulting in hospital admission	0.4 (0.8)	0.4 (0.7)	0.4 (0.8)	0.4 (0.8)	0.3 (0.7)	0.4 (0.9)
Patients with ≥1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)
Total asthma symptom score	2.68 (1.07)	2.72 (1.02)	2.70 (1.11)	2.74 (1.08)	2.67 (1.01)	2.68 (1.09)
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)
AQLQ(S)+12 score‡	3.90 (1.02)	3.93 (0.98)	3.94 (1.00)	3.87 (0.99)	3.93 (1.00)	3.93 (0.97)
Current smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Nicotine pack-years	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	6.0 (0–9)	5.0 (0–9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. Missing data is not accounted for in this table. ICS=inhaled corticosteroids. LABA=long-acting β2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

§ Current smoker or former smoker with a smoking history of ≥10 packs per year.

* Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other.

† Low numbers represent better symptom control.

‡ High numbers suggest better quality of life.

CALIMA

A total of 1,306 patients were randomised and received treatment in the CALIMA trial. Patient demographics and baseline clinical characteristics were balanced across treatment groups and by eosinophil count (at least 300 cells per μL versus less than 300 cells per μL) (Table 14).

Table 14: Baseline patient characteristics in the CALIMA trial

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)
Age (years)	48.8 (15.1)	50.0 (13.6)	49.0 (14.3)	48.5 (14.1)	50.1 (13.1)	49.6 (13.0)
Sex						
Male	176 (40%)	155 (36%)	168 (38%)	103 (42%)	82 (34%)	101 (42%)
Female	264 (60%)	270 (64%)	273 (62%)	145 (58%)	159 (66%)	138 (58%)
Race						
White	372 (85%)	360 (85%)	369 (84%)	213 (86%)	209 (87%)	203 (85%)
Black or African American	14 (3%)	10 (2%)	15 (3%)	8 (3%)	5 (2%)	8 (3%)
Asian	53 (12%)	55 (13%)	55 (12%)	27 (11%)	27 (11%)	28 (12%)
Other*	1 (<1%)	0	2 (<1%)	0	0	0
Hispanic or Latino ethnicity	92 (21%)	104 (24%)	104 (24%)	52 (21%)	56 (23%)	52 (22%)
BMI (kg/m^2)†	28.9 (6.5)	28.7 (6.8)	28.8 (6.5)	29.0 (6.1)	29.1 (7.3)	28.6 (6.1)
Local eosinophil count (cells per µL)†	371 (0–4494)	370 (20–2420)	400 (0–2600)	510 (300–4494)	500 (300–2420)	500 (300–2600)
Central eosinophil count (cells per µL)†	370 (0–4150)	350 (0–2800)	350 (0–2260)	490 (30–4150)	470 (0–2800)	475 (10–2260)
Prebronchodilator FEV_1 (L)†	1.771 (0.645)	1.757 (0.602)	1.759 (0.641)	1.815 0.648)	1.75 (0.570)	1.758 (0.622)
Prebronchodilator FEV_1 (% predicted normal)†	58.0% (14.9)	58.9% (14.8)	57.9% (14.9)	58.2% (13.9)	59.1% (13.7)	57.0% (14.2)
FEV_1/FVC prebronchodilator†	61 (13)	61 (12)	60 (13)	60 (12)	61 (12)	60 (13)
Reversibility†	20% (−18 to 814)	20% (−24 to 809)	20% (−13 to 171)	20% (−9 to 133)	20% (−24 to 124)	20% (−13 to 171)
ACQ-6 score‡	2.69 (0.92)	2.69 (0.91)	2.75 (0.93)	2.75 (0.94)	2.70 (0.91)	2.80 (0.95)
Time since asthma diagnosis (years)	16.2 (1.2–69.9)	15.8 (1.2–69.2)	16.8 (1.1–64.6)	17.0 (1.3–69.9)	15.6 (1.3–66.2)	16.1 (1.2–58.2)
Number of exacerbations in the past 12 months	2.7 (1.6)	2.7 (1.9)	2.7 (1.4)	2.8 (1.7)	2.8 (1.7)	2.7 (1.3)

2 (%)	288 (65.5)	280 (65.9)	287 (65.1)	151 (60.9)	148 (61.4)	144 (60.3)
3 (%)	93 (21.1)	89 (20.9)	93 (21.1)	56 (22.6)	54 (22.4)	59 (24.7)
≥4 (%)	59 (13.4)	55 (12.9)	60 (13.6)	41 (16.5)	38 (15.8)	36 (15.1)
Number resulting in ED visit	0.3 (1.2)	0.3 (0.8)	0.2 (0.7)	0.4 (1.4)	0.3 (0.9)	0.2 (0.6)
Patients with ≥1 exacerbations resulting in emergency department visit	62 (14%)	60 (14%)	56 (13%)	36 (15%)	35 (15%)	31 (13%)
Number resulting in hospital admission	0.3 (0.8)	0.2 (0.5)	0.3 (0.7)	0.3 (0.7)	0.2 (0.5)	0.3 (0.6)
Patients with ≥1 exacerbations resulting in hospital admission	72 (16%)	65 (15%)	78 (18%)	44 (18%)	42 (17%)	43 (18%)
Total asthma symptom score†	2.71 (1.04)	2.73 (1.02)	2.79 (1.06)	2.71 (1.06)	2.69 (0.98)	2.76 (1.06)
Diagnosis of allergic rhinitis	248 (56%)	242 (57%)	227 (51%)	147 (59%)	136 (56%)	125 (52%)
Nasal polyps	73 (17%)	59 (14%)	65 (15%)	55 (22%)	40 (17%)	53 (22%)
Atopic (based on Phadiatop test)	286 (65%)	264 (62%)	278 (63%)	164 (66%)	151 (63%)	149 (62%)
History of omalizumab treatment†	14 (3%)	12 (3%)	12 (3%)	9 (4%)	7 (3%)	7 (3%)
AQLQ(S)+12 score†§	3.96 (1.03)	3.98 (0.96)	3.85 (1.02)	3.93 (1.04)	3.99 (0.98)	3.87 (1.05)
Smoking history						
Never	349 (79%)	325 (76%)	348 (79%)	203 (82%)	175 (73%)	185 (77%)
Current	2 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)
Former	89 (20%)	100 (24%)	90 (20%)	44 (18%)	66 (27%)	53 (22%)
Smoking pack year (years)¶	5 (0–9)	5 (0–9)	5 (0–45)	4 (0–9)	5 (0–9)	4.5 (0–45)

Data are mean (SD), median (range), or n (%). ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroids. LABA=long-acting β2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).
*Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other.
†Data not available for all randomised patients.
‡The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β2-agonist use on a 0–6 scale (low numbers represent better control).
§The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale (greater numbers indicate better quality of life).
¶For current and former smokers. Missing data is not presented.

ZONDA

A total of 220 patients underwent randomisation and received study treatment in the ZONDA trial. Baseline characteristics were balanced between arms, with the exception of the median baseline blood eosinophil count, which was lower in the benralizumab 30 mg Q4W and Q8W groups compared with the placebo group (Table 15).

Table 15: Baseline patient characteristics in the ZONDA trial

Characteristic	Placebo (N=75)	Benralizumab Q4W (N=72)	Benralizumab Q8W (N=73)
Age (years)	49.9±11.7	50.2±12.0	52.9±10.1
Female sex, n (%)	48 (64)	40 (56)	47 (64)
White race, n (%)	70 (93.3)	69 (95.8)	66 (90.4)
BMI (kg/m^2)†	28.7±5.2	29.8±6.8	30.2±6.5
Blood eosinophil count			
Median count (range), cells/mm^3 ††	535 (160 - 4550)	462 (160 - 1740)	437 (154 - 2140)
Distribution, n (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)
FEV_1 before bronchodilation			
Value, litres	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation, %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (-5.4 - 93.4)	18.2 (-3.0 - 126.0)	22.6 (-3.4 - 88.0)
ACQ-6 score ‖	2.7±1.0	2.6±1.1	2.4±1.2
Median time since asthma diagnosis (range), yr	10.5 (1.1 - 54.5)	13.3 (1.2 - 52.3)	16.3 (1.3 - 53.0)
Number of exacerbations in previous 12 months	2.5±1.8	2.8±2.0	3.1±2.8
1	24 (32.0)	24 (33.3)	21 (28.8)
2	22 (29.3)	19 (26.4)	23 (31.5)
3	18 (24.0)	9 (12.5)	9 (12.3)
≥4	11 (14.7)	20 (27.8)	20 (27.4)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Median smoking history (range), pack-yr	6.0 (1 - 9)	5.5 (2 - 9)	5.0 (1 - 8)
Median oral glucocorticoid dose (range), mg/day			
At trial entry‡	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)
At end of run-in phase	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)

Mean inhaled glucocorticoid dose (range), µg/day	1232 (250 - 5000)	1033 (250 - 3750)	1192 (100 - 3250)
Leukotriene-receptor antagonist, n (%)	25 (33)	28 (39)	29 (40)

* Plus–minus values are means ±SD.
FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.
§ The percentage reversibility of the FEV_1 was calculated with the use of FEV_1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV_1 −prebronchodilation FEV_1]÷prebronchodilation FEV_1)×100. ¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.
‖ The Asthma Control Questionnaire 6 (ACQ-6)17 is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.
** The Asthma Quality of Life Questionnaire (standardised) for persons 12 years of age or older (AQLQ[S]+12)18 is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.
†† Patients were stratified at randomisation according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.

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

The statistical analysis for SIROCCO, CALIMA, and ZONDA is summarised in and discussed in further detail below.

Table 16: Summary of statistical analyses

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SIROCCO	Assess differences in exacerbation rates between benralizumab and placebo	ITT analysis using a negative binomial model for the primary endpoint, with adjustment for treatment, region, exacerbations in the previous year (two, three, or four or more), and OCS use	252 patients with blood eosinophil counts ≥300 cells per µL per treatment group (756 total) were needed for 90% power to detect a 40% reduction in annual exacerbation rate in both benralizumab dosage regimens compared with placebo	Patients who discontinued the study were followed up for subsequent visits. Sensitivity analyses were conducted to assess the impact of missing data on the primary and key secondary endpoints
CALIMA			228 patients with blood eosinophil counts ≥300 cells per µL per treatment group (684 total) were needed to achieve 90% power to detect a 40% reduction in the annual asthma exacerbation rate for both benralizumab dosage regimens versus placebo	

ZONDA	Assess differences in OCS dose reduction between benralizumab and placebo	ITT analysis using a Wilcoxon rank-sum test for the primary endpoint	70 patients per group was needed to achieve 86% power to detect a difference in the primary endpoint between each benralizumab group and placebo	The proportion of patients with missing data was low and similar across treatment groups; sensitivity analysis to assess the impact of missing data was not conducted

Hypothesis objective

In both SIROCCO and CALIMA, for each of the two benralizumab dosing regimens, the null hypothesis was that the exacerbation rate on benralizumab was equal to the exacerbation rate on placebo.

In ZONDA, the null hypothesis was that the reduction in OCS dose on benralizumab was equal to that on placebo, for each of the two benralizumab dosing regimens.

Sample size

SIROCCO

For the primary efficacy analysis, approximately 252 patients with blood eosinophil counts at least 300 cells per µL per treatment group (756 total) were needed for 90% power to detect a 40% reduction in annual exacerbation rate in both benralizumab dosage regimens compared with placebo, assuming a two-sided 4% α and an annual placebo exacerbation rate of 0.88 events per patient, based on phase 2b data. The sample size calculation was based on simulations and a negative binomial shape parameter of 0.9, on the basis of corresponding data from phase 2b trial results. A total enrolment of 1,134 adults and adolescents for randomisation was needed, including the enrolment of 126 patients per group (378 total) for the less than 300 cells per µL blood eosinophil cohort.

CALIMA

Approximately 228 patients needed to be randomised to each treatment group (totalling roughly 684 patients) to achieve 90% power to detect a 40% reduction in the annual asthma exacerbation rate in patients with baseline blood eosinophil counts 300 cells per μL or greater, for both benralizumab dosages versus placebo. The sample size calculation assumed two-sided 4% α-level tests, an annual placebo exacerbation rate of 0.88 events per patient based on published data and an exposure-response analysis of phase 2b study data, and a negative binomial shape parameter of 0.9. To maintain a 2:1 ratio of patients with blood eosinophil counts of 300 cells per μL or greater and less than 300 cells per μL, enrolment of 114 patients receiving high-dosage inhaled corticosteroids plus LABA with blood eosinophil counts less than 300 cells per μL was targeted per treatment group. Approximately 270 patients receiving medium-dosage inhaled corticosteroids plus LABA were expected to be recruited.

ZONDA

An estimated 70 patients per group was required for the trial to detect a difference in the primary endpoint between each benralizumab group and the placebo group, with 86% power by means of a Wilcoxon rank-sum test with a two-sided level of 5%. This estimation was based on simulations that used data from the Steroid Reduction with Mepolizumab Study (SIRIUS), which yielded a median percentage reduction from baseline of 50% in the glucocorticoid dose in the active-treatment group, as compared with no reduction in the placebo group. Approximately 60 patients with a blood eosinophil count of at least 150 cells to less than 300 cells per cubic millimetre and 150 patients with a blood eosinophil count of 300 cells or more per cubic millimetre were targeted to undergo randomisation.

Randomisation and blinding

SIROCCO

All adult patients, and adolescent patients enrolled at non-European Union (EU) sites, were randomly assigned (1:1:1) to one of three 48-week treatment groups: subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses given 4 weeks apart), or matching placebo. Adolescent patients enrolled at sites in the EU were randomly assigned to one of two treatment groups: subcutaneous benralizumab 30 mg Q8W (first three doses given Q4W) or matching placebo to accommodate a request by the Paediatric Committee at the European Medicines Agency to limit drug burden in adolescents.

Each patient was assigned a unique enrolment number and randomisation code by an interactive web-based voice response system. Randomisation was stratified by age group (adult or adolescent), country (in adults) or region (within the EU and outside the EU for adolescents), and blood eosinophil counts. The randomisation stratified patients (2:1) for blood eosinophil counts of at least 300 cells per μL and less than 300 cells per μL, which were measured at a local laboratory. The randomisation was stratified to enrich the study population with patients most likely to benefit from benralizumab treatment and to provide insight into efficacy in patients with low baseline blood eosinophil counts. Randomisation codes were assigned by the study investigator sequentially in each stratum as patients became eligible for randomisation, until each stratum was full.

The study was planned with a double-blind, double-dummy design to ensure masking throughout. The identity of the treatment allocation was not made available to the patients, investigators involved in patient treatment or clinical assessment, or study funder. Placebo solution was visually matched with benralizumab solution.

CALIMA

Eligible adult patients from all regions and adolescent patients from outside of the European Union were randomly assigned (1:1:1) to receive 56-week, double-blind treatment with either benralizumab 30 mg once every 4 weeks (Q4W), benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period (hereafter referred to as the Q8W regimen), or placebo. As for SIROCCO, patients aged 12–17 years enrolled within the European Union were randomly assigned (1:1) to receive double-blind treatment with benralizumab 30 mg Q8W or placebo.

Similarly, patients were assigned to treatment groups using an interactive web-based voice response system. Randomisation was stratified by inhaled corticosteroids dosage at enrolment (high or medium), geographic region, age group, and peripheral blood eosinophil count at enrolment. Patients were recruited with blood eosinophils 300 cells per μL or greater and less than 300 cells per μL at screening in a ratio of approximately 2:1, respectively. The study investigator assigned randomisation codes sequentially in each stratum as patients became eligible for randomisation, until each stratum was full.

To preserve blinding, patients and study centre staff were masked to treatment allocation, placebo solution was visually matched with benralizumab solution, and both placebo and benralizumab were provided in accessorised (needle guards and finger phalanges), pre-filled syringes.

ZONDA

Patients were randomised to receive benralizumab 30 mg every 4 weeks, benralizumab 30 mg every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits), or placebo every 4 weeks.

Patients underwent randomisation in a 1:1:1 ratio, with the use of an interactive Web- or voice-response system, and were stratified according to eosinophil count (≥150 to <300 cells per cubic millimetre vs. ≥300 cells per cubic millimetre) and country. Investigators and patients were blinded to the trial group assignments, with placebo visually matched to benralizumab.

Outcome assessments

SIROCCO and CALIMA

The primary efficacy endpoint was analysed using a negative binomial model, with adjustment for treatment, region, exacerbations in the previous year (two, three, or four or more), and oral corticosteroid use at time of randomisation. The estimated treatment effect (i.e., rate ratio of benralizumab vs placebo), corresponding 95% CI, and two-sided p value for the rate ratio were calculated. The annual exacerbation rate and corresponding 95% CIs within each treatment group were also calculated. Prespecified subgroup analyses assessed the exacerbation rate in subgroups of clinical relevance. A post-hoc analysis was also conducted in the primary analysis population for the purposes of this submission, to assess the treatment effect of a history of at least three exacerbations experienced by patients in the previous year using a separate negative binomial model with adjustment for treatment, region, oral corticosteroid use, and number of previous exacerbations.

The key secondary endpoints were analysed using a mixed-effects model for repeated measures analysis, with adjustment for treatment, region, baseline value, oral corticosteroid use at time of randomisation, visit, and visit × treatment. Least-squares means, treatment differences in least-squares means, 95% CIs, and p values were calculated. Other continuous secondary efficacy endpoints were analysed using a mixed-effects model for repeated measures analysis. Time to first asthma exacerbation was analysed using a Cox proportional hazard model, with adjustment for treatment, region, exacerbations in the previous year, and oral corticosteroid use at time of randomisation.

To account for multiplicity to test the primary endpoint and two key secondary endpoints (i.e., change from baseline in FEV_1 and asthma symptom score) for each of the two benralizumab dosing regimens, a multiple testing procedure was followed to control the overall type I error rate. The testing procedure permitted two tests of annual asthma exacerbation rate (one test for each dosing regimen vs placebo) at the family-wise error rate of 0·04 using a Hochberg procedure. If both p values were less than 0·04, then the two key secondary endpoints could be tested for both dosing regimens at a family-wise error rate of 0·05 using a Holm procedure.

All efficacy analyses were conducted on the intention-to-treat (ITT) population; that is, all randomly assigned patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. Safety analyses were based on the actual treatment regimen received and included all patients who received at least one dose of study drug. All analyses were conducted using SAS version 9.2.

ZONDA

For the primary endpoint, benralizumab was compared with placebo using a Wilcoxon rank-sum test. To control the overall type I error rate, multiple comparisons were accounted for by using the Hochberg procedure. A sensitivity analysis for the assessment of the primary endpoint was conducted with a proportional-odds model, with controls for trial group, geographic region (Asia, Central Europe and Eastern Europe, Western Europe and Turkey, North America, and the rest of world), and baseline oral glucocorticoid dose.

A Cochran-Mantel-Haenszel test, with adjustment for geographic region, was used to analyse secondary endpoints regarding reductions in the oral glucocorticoid dose. A negative binomial model, with adjustment for trial group, geographic region, and number of exacerbations in the previous year, with an offset term of the logarithm of the follow-up time was used to calculate annual exacerbation rates in the trial groups. Treatment effects were described with the use of rate ratios. The analyses of the secondary endpoints were not controlled for multiple comparisons and were presented with nominal P values. Results for exploratory variables were analysed with the use of descriptive statistics according to trial group, unless otherwise indicated. Data were analysed with the use of SAS software, version 9.2.

Data management, withdrawals

In all three trials, patients were permitted to discontinue treatment and assessments at any time at the discretion of the investigators. Patients were also free to withdraw from the study at any time, without prejudice to further treatment. Patients who prematurely discontinued treatment were to complete a premature discontinuation visit, and were encouraged to remain in the study to complete all subsequent visits and assessments. Patients who were not willing to continue participating in the study were to return to the study centre one last time at around 12 weeks after the last dose of treatment for final study-related assessments. Reasons for withdrawal were recorded.

In SIROCCO and CALIMA, missing data occurred when patients withdrew from the study or when data were not available at certain visits (for FEV_1 and total asthma symptom score). Sensitivity analyses were conducted to assess the impact of missing data on the primary and key secondary endpoints. Three multiple imputation methods (missing at random [MAR], partial-dropout reason-based multiple imputation [partial-DRMI], and DRMI) were used to assess robustness to missing data for these endpoints. The results of all three methods were consistent with the results of the primary efficacy analysis, indicating that the results of the studies were robust to missing data. In ZONDA, the proportion of patients with missing data was low and similar across treatment groups, and the optional sensitivity analysis to assess the impact of missing data was not conducted.

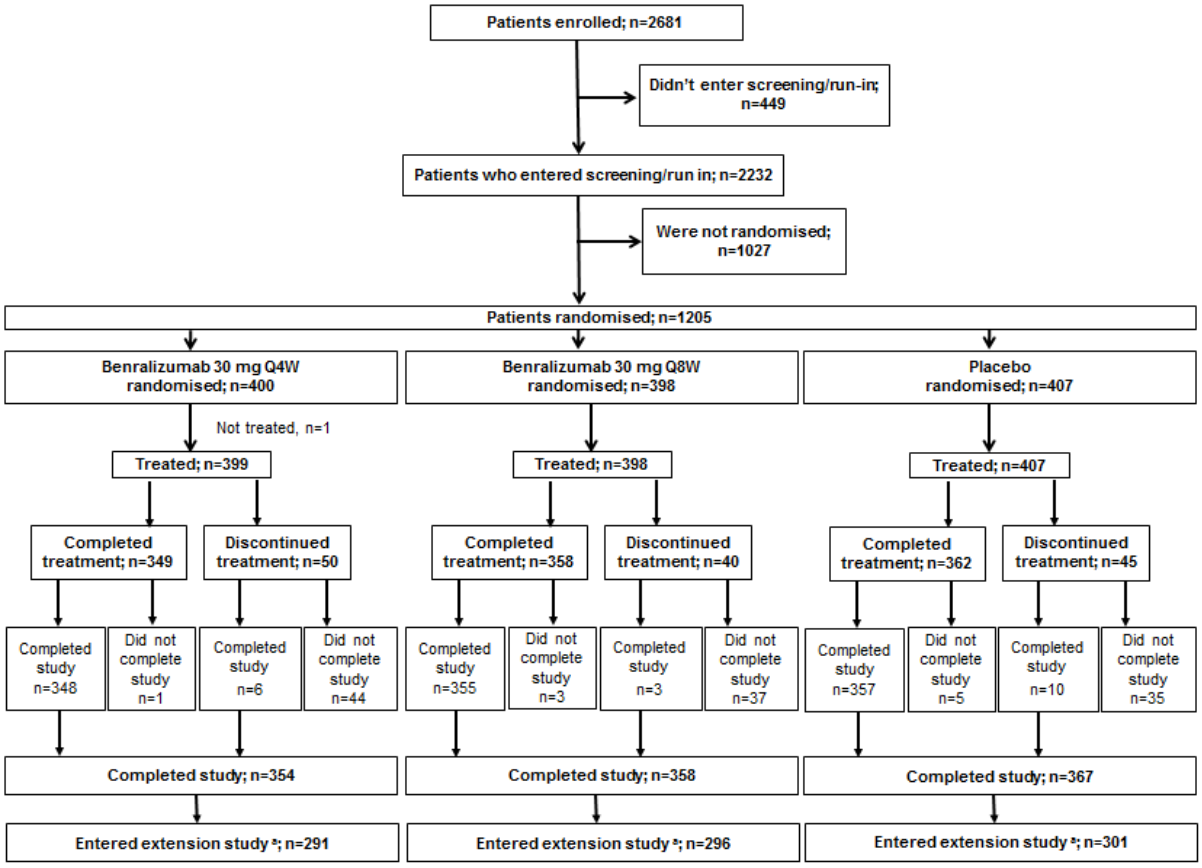
Participant flow

SIROCCO

A total of 2,681 patients were enrolled in the SIROCCO trial; 2232 patients entered screening/run-in, and 1,205 patients were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. One patient who was randomised did not receive treatment and was considered lost to follow-up; all other randomised patients received their allocated treatment.

Overall, 1,069 (88.7%) patients completed treatment and 135 (11.2%) patients discontinued treatment (Figure 12). The proportions of patients who discontinued treatment were similar across the groups. The most frequent reasons for discontinuation of study treatment were patient decision (4.6%), other (2.2%), and AE (1.8%). Most (116 of 135) patients who discontinued treatment also discontinued the study.

Figure 12: Participant flow in the SIROCCO trial



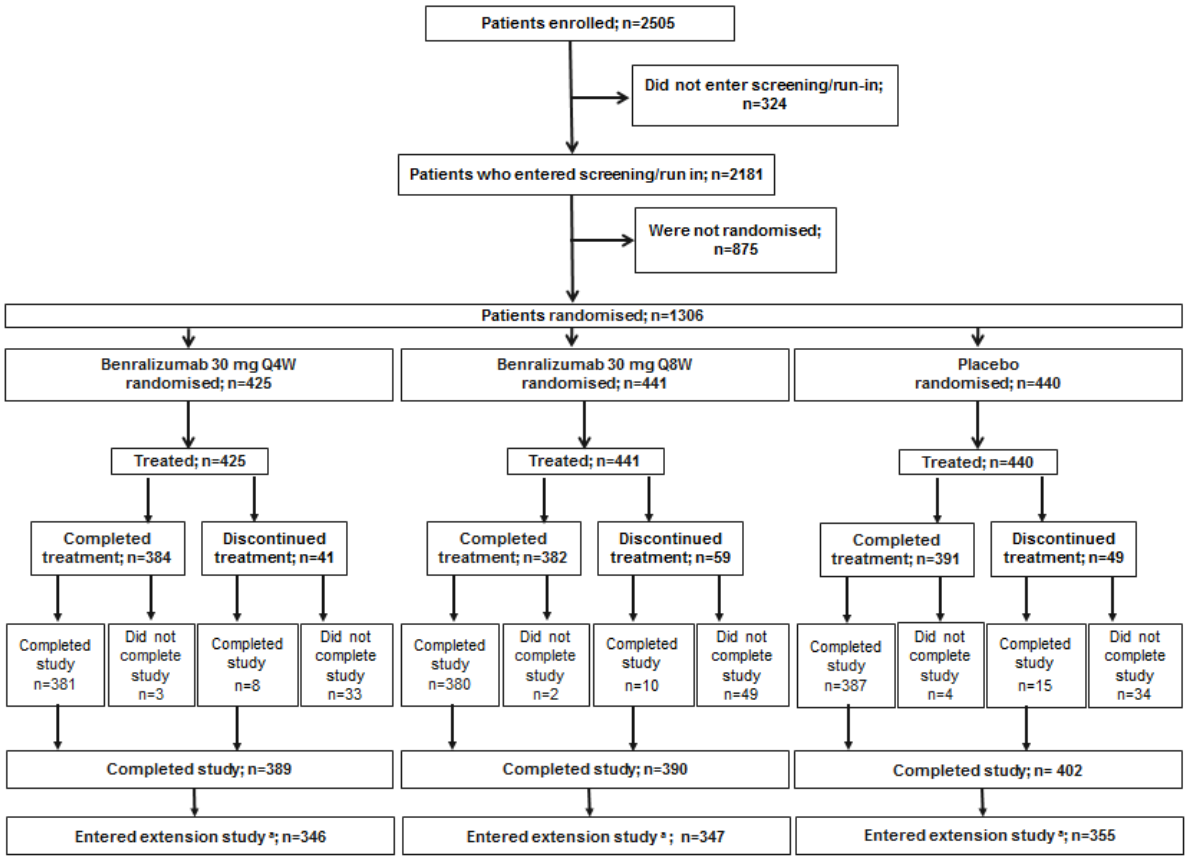
A total of 91 patients (7.6%) in the full analysis set (FAS – including all patients who underwent randomisation) had at least one important protocol deviation: 34 (8.5%) in the benralizumab 30 mg Q4W group, 28 (7.0%) in the benralizumab 30 mg Q8W group, and 29 (7.1%) in the placebo group. The most frequent important protocol deviations overall were deviations related to inclusion/exclusion criteria (7.1%), of which the most common deviation was a pre-bronchodilator FEV_1 ≥80% (or ≥90% for adolescents) at randomisation (4.1%). Overall, the occurrence of important protocol deviations was similar across groups and was considered not to impact the interpretation of the study results.

CALIMA

Of the 2,505 patients enrolled in the CALIMA trial, 2181 patients entered screening/run-in, and 1,306 were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. All randomised patients (comprising the FAS) received at least one dose of study drug.

A total of 1,157 (88.6%) patients completed treatment with study drug and 149 (11.4%) patients discontinued treatment (Figure 13). The proportions of patients who discontinued treatment were similar across groups, with the most frequent reasons for discontinuation of study treatment overall being patient decision (4.8%), other (2.5%), and AE (1.7%). Most (116 of 149) patients who discontinued treatment also discontinued the study.

Figure 13: Participant flow in the CALIMA trial



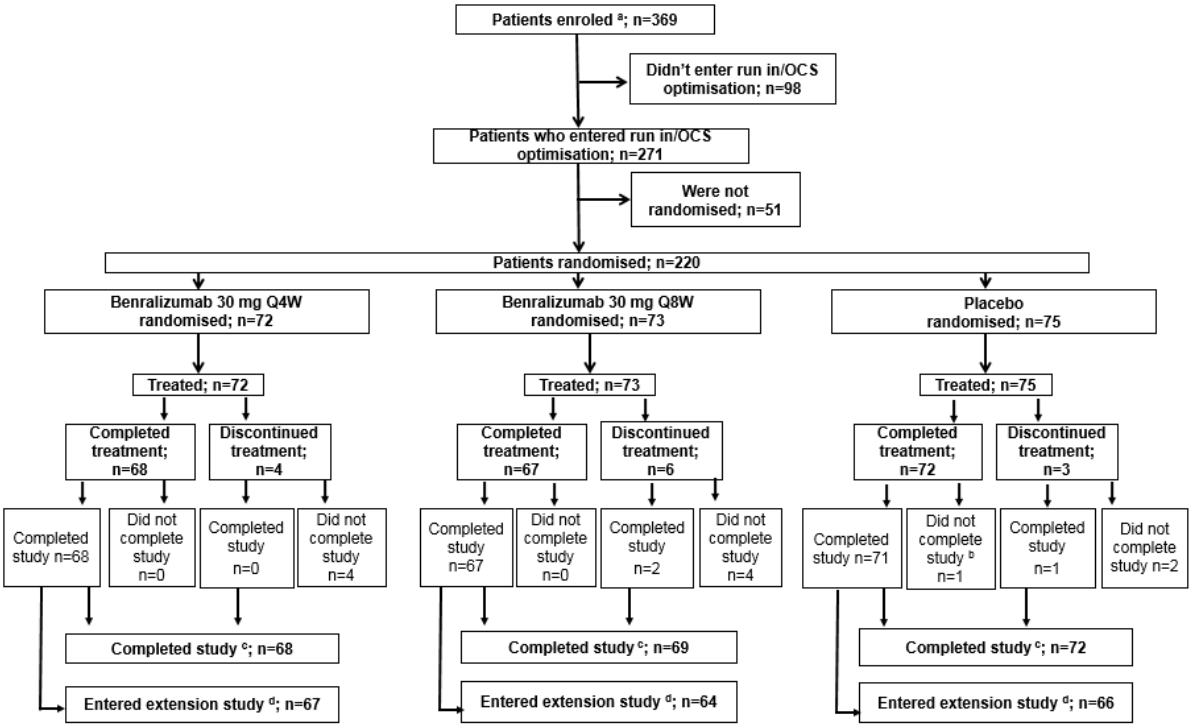
Overall, 105 patients (8.0%) had at least one important protocol deviation during the study; the incidence was higher in the benralizumab 30 mg Q8W group (10.9%) compared with the benralizumab 30 mg Q4W (6.6%) or placebo (6.6%) groups. This difference was driven by the increased incidence of patients receiving incorrect study treatment (in the form of additional benralizumab doses instead of placebo doses after week 8, affecting 22 patients [5.0%] in the benralizumab 30 mg Q8W group). Other notable important protocol deviations related to inclusion/exclusion criteria (6.4%), of which the most common deviation was a pre-bronchodilator FEV_1 ≥80% (or ≥90% for adolescents) at randomisation (4.2%). Overall, the occurrence of important protocol deviations was considered not to impact the interpretation of the study results.

ZONDA

A total of 369 patients were enrolled in the ZONDA trial, of whom 271 entered run-in/OCS optimisation. Of these, 220 patients were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo and received at least one dose of study drug.

Overall, 207 (94.1%) patients completed their allocated treatment, and 13 (5.9%) patients discontinued treatment (Figure 14). The proportion of patients who discontinued treatment was similar across the groups, with 5 (2.3%) discontinuing due to AEs, 5 (2.3%) due to patient decision, 2 (0.9%) due to the development of study-specific discontinuation criteria, and 1 (0.5%) due to other. Most (10 of 13) patients who discontinued treatment also withdrew from the study.

Figure 14: Participant flow in the ZONDA trial



A total of 54 patients (24.5%) in the FAS (comprising all randomised patients) had at least 1 important protocol deviation, with a greater percentage in the placebo group (27 [36.0%] patients) compared with the benralizumab 30 mg Q4W (15 [20.8%] patients) and Q8W groups (12 [16.4%] patients). The most frequent important protocol deviations overall were deviations related to OCS dose titration criteria which could have impacted the final OCS dose (22.3%) and inclusion/exclusion criteria (4.5%).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment

Table 17 contains a summary of the quality assessment for the clinical trials, based on the NICE submission template user guide. Please refer to Appendix D for a complete quality assessment.

Table 17: Summary of the quality assessment for the key clinical trials

	SIROCCO and CALIMA	ZONDA
Was randomisation carried out appropriately?	Yes – each patient assigned unique enrolment number and randomisation code by an interactive web-based voice response system	
Was the concealment of treatment allocation adequate?	Yes – AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation were not aware of the treatment allocation	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – patient demographics and baseline clinical characteristics were balanced across treatment groups and by eosinophil count (at least 300 cells per µL versus less than 300 cells per µL)	Baseline characteristics were balanced between arms, with the exception of median baseline blood eosinophil count, which was lower in the benralizumab 30 mg Q4W and Q8W groups compared with the placebo group
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – placebo solution was visually matched with benralizumab solution. Both benralizumab and placebo were provided in an accessorised pre-filled syringe	
Were there any unexpected imbalances in drop-outs between groups?	No – the proportions of patients who discontinued treatment were similar across groups	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all key pre-specified endpoints were reported in the clinical study reports and/or publications	
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 – all analyses conducted on the ITT population. Sensitivity analyses were conducted to assess the impact of missing data Three multiple imputation methods (MAR, partial-DRMI, and DRMI) were used to assess robustness to missing data	Yes – all analyses conducted on the ITT population. Sensitivity analyses to account for missing data were not conducted due to the low proportion of missing data

Please see Appendix D for full details of the quality assessment.

Applicability to clinical practice

It is expected that the results of the Phase 3 trials will be broadly applicable to clinical practice in England. Maintenance therapy at baseline in the Phase 3 clinical trials was in-line with recommended UK guidelines, i.e., high-dose ICS plus LABA ± OCS based on BTS/SIGN recommendations, and patients continued to receive their asthma-controller medications concomitantly throughout the trials. Although the trials contained few UK patients, baseline characteristics were comparable to those in previously published analyses of patients with severe asthma in the UK for most characteristics (Table 18) (Heaney et al. 2010, Kerkhof et al. 2017).

Key trial endpoints including exacerbation rates, lung function, OCS use, and PRO measures are also used to assess the efficacy of treatment in clinical practice, and reflect patient-relevant outcomes. Results for exacerbation reductions with benralizumab in European patients were numerically favourable, compared with the overall population in SIROCCO and CALIMA (potentially due to differences in baseline exacerbation rates), while OCS reductions in ZONDA were directionally consistent between European patients and the overall population (Section B.2.6). In addition, relevance of the clinical data and subgroup positioning was explored and confirmed through engagement with UK clinicians, at an AstraZeneca-sponsored advisory board (AstraZeneca 2017).

Table 18: Comparison of baseline characteristics between the Phase 3 benralizumab trials and published literature

	SIROCCO	CALIMA	ZONDA	(Heaney et al. 2010)	(Kerkhof et al. 2017)
Patient population	Severe asthma treated with high-dosage ICS+LABA	Severe asthma treated with medium- or high-dosage ICS+LABA*	Eosinophilic asthma treated with high-dose ICS+LABA, +OCS	Refractory UK asthma patients (ATS definition)	Severe uncontrolled eosinophilic UK asthma patients
Mean age, years	48.8	49.2	51.0	NR	55.8
Female sex, %	66.1	61.8	61.4	63.1	66.4
White race, %	72.6	84.3	93.2	90.6	NR
Mean BMI, kg/m^2	28.78	28.77	29.58	28	NR
Mean local eosinophil count	472	472	575	NR	NR
Never-smoker, %	80.4	78.3	79.1	61.0	50.8
Prebronchodilator FEV_1, L	1.665	1.762	1.846	1.90	NR
Reversibility, %	25.7	39.2	24.1	NR	NR

Median time since diagnosis, years	14.76	16.11	12.18	NR	NR
Mean exacerbations in past year, n	2.9	2.7	2.8	NR	2
Mean ACQ-6 score	2.81	2.71	2.56	NR	NR
Diagnosis of allergic rhinitis, %	53.7	54.9	50.9	36.6	20.7
Nasal polyps, %	19.7	15.1	31.8	13.4	12.8
Eczema, %	12.0	10.0	7.3	27.0	34.0
History of omalizumab treatment, %	7.3	2.9	14.1	NR	0^
ICS/LABA therapy, %	100	100	100	NR	100
OCS users, %	16.3	9.3	100	41.7	16.6

* Note that although medium-dose patients were included, primary analyses were conducted on patients receiving high-dose
^ Defined as ≥1 prescription during baseline in this study
ATS: American Thoracic Society; BMI: Body mass index; FEV1: Forced expiratory volume in 1 second; ICS/LABA: Inhaled corticosteroid + long-acting beta-agonist therapy; OCS: Oral corticosteroid

B.2.6 Clinical effectiveness results of the relevant trials

In-line with the licensed indication, only the results for the licensed dose (Q8W) are presented below, and unless otherwise specified, all results are presented for patients with baseline blood eosinophil counts at least 300 cells per μL, and on high dose ICS/LABA with or without OCS. While the key results are presented from each trial, the focus of the submission is on the patient subgroup for which a NICE recommendation is sought (i.e., patients with blood eosinophil count ≥300 cells per μL, and either ≥3 exacerbations needing systemic corticosteroids in the past 12 months, or ≥6 months previous treatment with OCS), with subgroup analyses from SIROCCO, CALIMA (pooled), and ZONDA demonstrating the safety and efficacy of benralizumab in this specific patient group.

Data for this section are sourced from the clinical trial publications (Bleecker 2016, FitzGerald 2016, Nair et al. 2017) and the clinical study reports (CSRs) for each trial.

SIROCCO

For the primary endpoint, benralizumab decreased the annual asthma exacerbation rate by 51% compared with placebo at week 48, with a rate ratio versus placebo of 0.49 (0.37–0.64; p<0.0001). Overall, 34.8% of patients treated with benralizumab Q8W experienced at least one exacerbation during the study period, compared with 50.6% of patients on placebo. In terms of key secondary endpoints, a significant improvement in lung function, as measured by pre-bronchodilator FEV_1 was observed (LS mean difference versus placebo of 159ml; p=0.0006) (Figure 15). Benralizumab also demonstrated improvements in asthma symptoms, as measured by total asthma symptom score (LS mean difference versus placebo of -0.25; p=0.0118) (Table 19), which, whilst statistically significant, did not reach the MCID.

Table 19: Primary and key secondary endpoint results in the SIROCCO trial

	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; p value)	-	0.49 (0.37–0.64; <0.0001)
Key secondary endpoints (48 weeks)		
Prebronchodilator FEV_1 (L)†		
Number of patients‡	261	264
LS mean change (number of patients§)	0.239 (233)	0.398 (235)
LS mean difference vs placebo (95% CI; p value)	-	0.159 (0.068 - 0.249; 0.0006)
Total asthma symptom score†¶		
Number of patients analysed‡	267	263
LS mean change (number of patients§)	−1.04 (180)	−1.30 (178)
LS mean difference vs placebo (95% CI; p value)	-	−0.25 (−0.45 - −0.06; 0.0118)
EQ-5D		
Number of patients analysed^	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference	[redacted]	[redacted]

EQ-5D= EuroQol 5 dimensions; ICS=inhaled corticosteroids. LABA=long-acting β2-agonsists. Q8W=every 8 weeks (first three doses Q4W). FEV_1=forced expiratory volume in 1 s. LS=least squares.

* Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.

† Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.

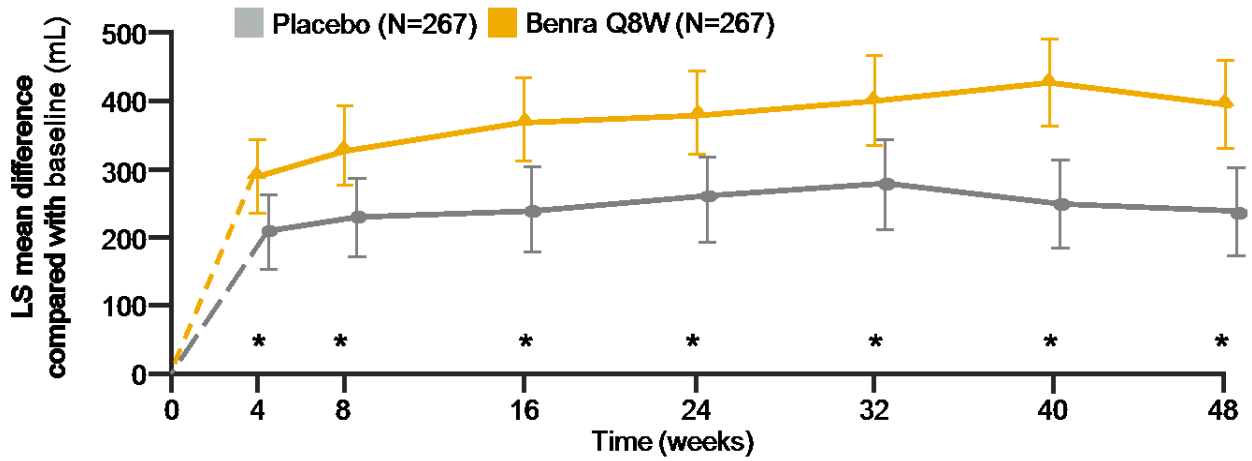
‡ Patients with a baseline and at least one post-baseline assessment.

§ Numbers of patients at 48 weeks.

¶ A decrease in score suggests an improvement

^ Excludes adolescents

Figure 15: FEV_1 change from baseline through Week 48 in SIROCCO



*P<0.05 for benra 30 mg Q8 weeks vs placebo.
Error bars represent 95% confidence intervals. P values are from the repeated measures analysis.
Benra=benralizumab; FEV_1=forced expiratory volume in 1 sec; LS=least squares; Q8W=every 8 weeks.

CALIMA

Benralizumab decreased the annual asthma exacerbation rate by 28% compared with placebo at week 56, with a rate ratio versus placebo of 0.72 (0.54–0.95; p=0.018). Overall, 39.7% of patients treated with benralizumab Q8W experienced an exacerbation during the study period, compared with 50.8% of patients on placebo. For key secondary endpoints, a significant improvement in lung function, as measured by pre-bronchodilator FEV_1 was observed (LS mean difference versus placebo of 116ml; p=0.0102) (Figure 16). Benralizumab also demonstrated improvements in asthma symptoms, as measured by total asthma symptom score (LS mean difference versus placebo of -0.23; p=0.0186) (Table 20).

Table 20: Primary and key secondary endpoint results in the CALIMA trial

	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; p value)	-	0.72 (0.54–0.95; 0.0188)
Key secondary endpoints (48 weeks)		
Prebronchodilator FEV_1 (L)†		
Number of patients‡	244	238
LS mean change (number of patients§)	0.215; 221	0.330; 211
LS mean difference vs placebo (95% CI; p value)	-	0.116 (0.028–0.204; 0.0102)
Total asthma symptom score†¶		
Number of patients analysed‡	247	237

LS mean change (number of patients§)	−1.16; 187	−1.40; 185
LS mean difference vs placebo (95% CI; p value)	-	−0.23 (−0.43 to −0.04; 0.0186)
EQ-5D		
Number of patients analysed^	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference (95% CI; p value)	[redacted]	[redacted]

Data for the primary endpoint are rate estimate (95% CI) or rate ratio (95% CI). Data for the secondary endpoint are mean change from baseline at week 56; n or mean difference (95% CI). EQ-5D= EuroQol 5 dimensions; FEV_1=forced expiratory volume in 1 s. LS=least squares. Q8W=once every 8 weeks (first three doses Q4W).

* Estimates calculated using a negative binomial model with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.

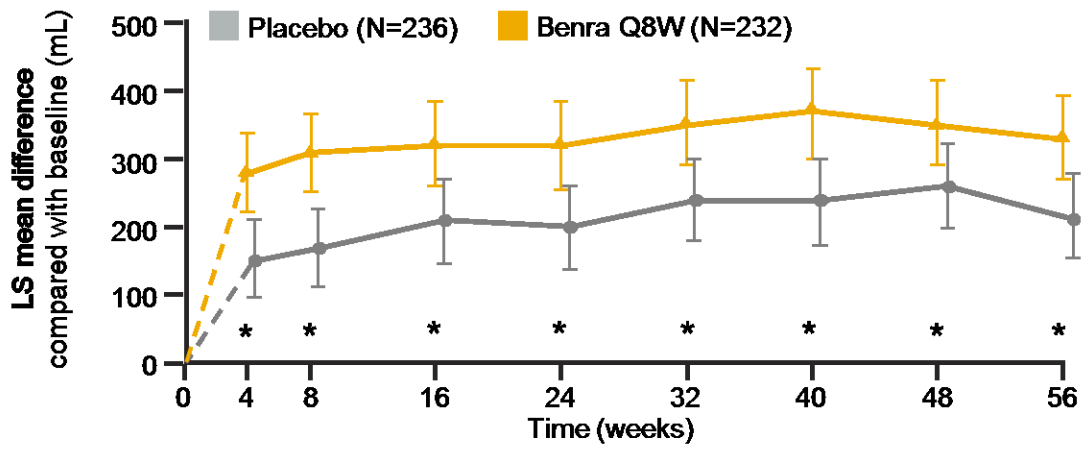
† Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.

‡ Key secondary endpoint; composite of daytime and night-time symptoms scored 0–6 overall (a decrease in score indicates improvement).

§ Numbers after semicolon are patients at 56 weeks

^ Excludes adolescents

Figure 16: FEV_1 change from baseline through Week 56 in CALIMA



*P<0.05 for Benra 30 mg Q8W.

Error bars represent 95% confidence intervals. *P* values are from the repeated-measures analysis.

Benra=benralizumab; FEV_1=forced expiratory volume in 1 sec; LS=least squares; Q8W=every 8 weeks.

Rationale for differences between SIROCCO and CALIMA: regional differences in exacerbation rates

Despite similar trial designs and populations included in the primary analyses, reductions in exacerbation rates were observed to be greater in SIROCCO than in CALIMA. As presented in the CALIMA publication (FitzGerald 2016), subgroup analyses suggested three key drivers for this observation: regional effect, exacerbation history, and background medication.

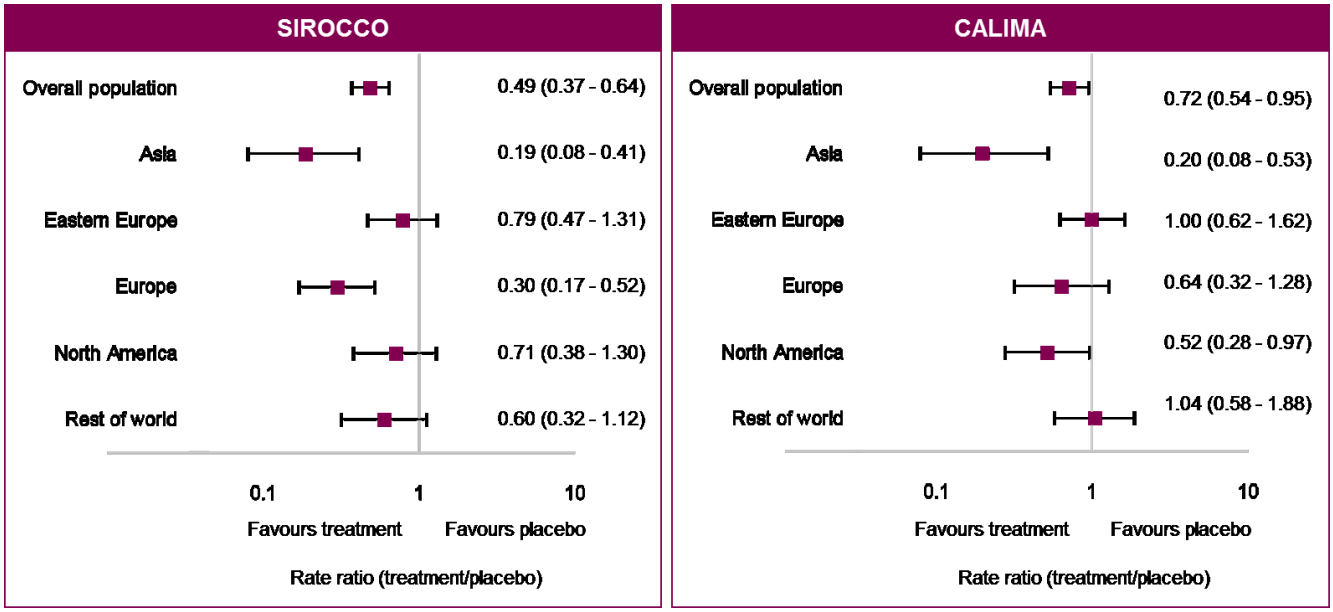
Heterogeneity in regional exacerbation rates in CALIMA might have contributed to the size of treatment effect of benralizumab to a greater extent in CALIMA than in SIROCCO. This finding was substantially the consequence of patients from Eastern Europe and South America who had fewer exacerbations in the year before study entry (i.e., less severe baseline disease). Essentially these patients had very low rates of exacerbations during the treatment period, irrespective of the treatment regimen.

In support of this explanation, we found that patients who had experienced 3 or more exacerbations in the previous year (i.e., greater asthma severity at baseline – see Section B.2.7) were under-represented in the Eastern Europe and South America regions, and had the greatest effects of benralizumab treatment. Exacerbation reductions in this subgroup of CALIMA patients (3 or more exacerbations in the year before study) reflect annual asthma exacerbation rate reduction results of the SIROCCO study – i.e., 51% for the Q8W regimen in CALIMA and 57% in SIROCCO.

In addition to regional heterogeneity and exacerbation history, the efficacy results of CALIMA seem to be affected by a strong placebo response. The exacerbation rate of patients in the placebo group during the treatment period of the trial was 0.93, far different from the exacerbation rate of 2.8 seen in the year prior to randomisation. This response could have led to an underestimation of the treatment benefit of benralizumab in CALIMA. Unlike other biologic clinical trials, the Sponsor provided background medication of high dose ICS/LABA to all patients during the entire clinical trial, which could also have contributed to the strong placebo response.

Differences in exacerbation rate reductions, by region, for both SIROCCO and CALIMA are presented in Figure 17. It should be noted that hazard ratios for European patients were numerically favourable compared with the overall population. However, analyses of exacerbation rates by region were explanatory and not powered to detect differences, with small n numbers in each group; correspondingly, confidence intervals are wider than in the overall population.

Figure 17: Exacerbation rate reduction, by geographical region in SIROCCO and CALIMA analyses (high-dosage ICS/LABA with blood eosinophils ≥300 cells/µL)



Pre-specified subgroup analysis. Values in parentheses represent 95% CIs. Statistical analysis model was a negative binomial mode, including covariates for treatment group, region, use of maintenance OCS, and number of exacerbations in the previous year. Europe encompasses Western Europe and Turkey.

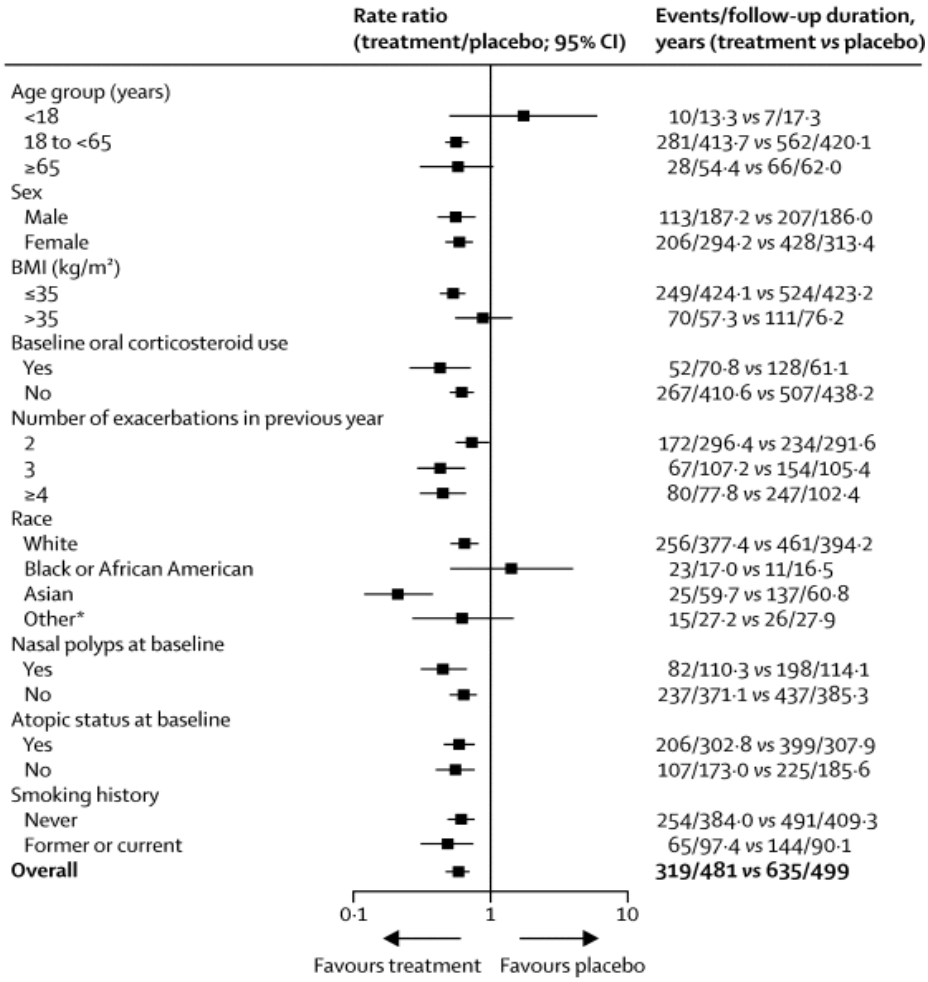
Pooled SIROCCO and CALIMA

A pre-specified pooled efficacy analysis of the SIROCCO and CALIMA trials was conducted to better understand the relationship between the clinical efficacy of benralizumab and baseline blood eosinophil counts and exacerbation history, and therefore identify which patients are most likely to benefit from treatment with benralizumab (FitzGerald et al. 2017). The similar design of the two studies allowed for the results to be pooled, with the log of each patient's corresponding follow-up time used as an offset variable to adjust for patients' having different exposure times during which the events occurred (i.e. differences in study durations). Patients on medium-dose ICS in CALIMA were excluded.

Results from 1204 patients in SIROCCO and 1091 patients in CALIMA on high-dose ICS plus LABA were included to give a total of 2295 patients in the pooled analysis. In patients with eosinophils ≥300 cells/µl, 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).

Previous exacerbations, baseline blood eosinophil counts, and baseline lung function indices were found to be consistent and influential predictors of exacerbation reduction (Figure 18 and Figure 19). Baseline lung function indices (especially reversibility) and eosinophil counts were also important predictors of FEV_1 change.

Figure 18: Analysis of the effect of patient baseline characteristics on the efficacy of benralizumab treatment



Data are from the ITT population from the high-dosage inhaled corticosteroid treatment cohorts from the SIROCCO and CALIMA studies (baseline blood eosinophils ≥300 cells per µL; full analysis set, pooled). AER was analysed using a negative binomial model.
AER=annual asthma exacerbation rate. BMI=body-mass index. Q8W=every 8 weeks (first three doses every 4 weeks).

Figure 19: Annual asthma exacerbation rates by baseline eosinophil count (full analysis set, pooled)

	Placebo (n=777)	Benralizumab Q8W (n=762)
≥0 cells per µL		
Number of patients analysed	770	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·55 to 0·75)
p value *vs* placebo	..	<0·0001
≥150 cells per µL		
Number of patients analysed	648	646
Rate estimate (95% CI)	1·14 (1·02 to 1·28)	0·72 (0·63 to 0·82)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·42 (−0·58 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·63 (0·53 to 0·74)
p value *vs* placebo	..	<0·0001
≥300 cells per µL		
Number of patients analysed	511	499
Rate estimate (95% CI)	1·14 (1·00 to 1·29)	0·65 (0·56 to 0·75)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·49 (−0·67 to −0·32)
Rate ratio *vs* placebo (95% CI)	..	0·57 (0·47 to 0·69)
p value *vs* placebo	..	<0·0001
≥450 cells per µL		
Number of patients analysed	306	298
Rate estimate (95% CI)	1·25 (1·06 to 1·47)	0·62 (0·51 to 0·76)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·63 (−0·87 to −0·39)
Rate ratio *vs* placebo (95% CI)	..	0·50 (0·38 to 0·64)
p value *vs* placebo	..	<0·0001

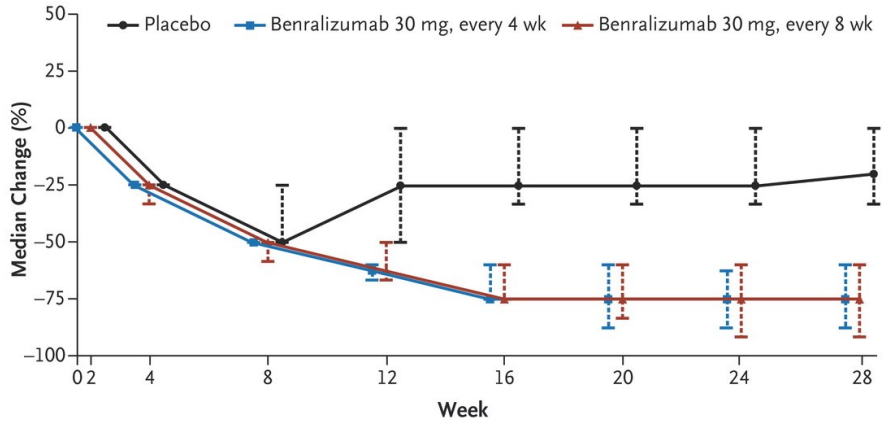
CI: Confidence interval; Q8W: Every 8 weeks

Based on this analysis, benralizumab was found to be more efficacious in patients who had experienced three or more exacerbations in the year before study entry (and eosinophil counts ≥300 cells per µL), than in those patients who had experienced two exacerbations. This informed the patient subgroup for which a NICE recommendation is sought (i.e., patients with blood eosinophil count ≥300 cells per µL, and either ≥3 exacerbations needing systemic corticosteroids in the past 12 months, or ≥6 months previous treatment with OCS) and is further discussed in Section B.2.7.

ZONDA

For the primary endpoint, benralizumab reduced the median final OCS dose by 75% from baseline, compared with a reduction of 25% in the OCS doses in the placebo group (p<0.001) (Figure 20). This translated to a Hodges-Lehman median treatment difference of 37.5% (95% CI 20.8 - 50.0).

Figure 20: Median change from baseline in oral glucocorticoid dose in the ZONDA trial



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

Error bars represent 95% confidence intervals. Values are slightly offset from each other at each time point for clarity.

The odds of a reduction in OCS dose were 4.12 times higher with benralizumab than with placebo (95% CI: 2.22 - 7.63; p<0.001). In addition, greater proportions of patients in the benralizumab Q8W group had a 90% to 100% reduction from baseline in daily OCS dose at Week 28 compared with those in the placebo group (37.0% versus 12.0%, respectively). When stratified by baseline OCS dose, patients on benralizumab receiving ≤10 mg/d OCS at baseline (n=38) had a median 100% reduction in OCS dose, compared with 25% for patients on placebo (n=39). In addition, 52% of patients eligible for a 100% reduction in OCS dose (i.e., those receiving ≤12.5mg/day at the end of the run-in phase) achieved this outcome in the benralizumab arm, compared with 19% in the placebo arm. All secondary outcomes related to reduction in the OCS dose were met.

In terms of other secondary outcomes of interest, the annual asthma exacerbation rate was 70% lower in the benralizumab Q8W group than in the placebo group (nominal p<0.001) (Table 21), with 23.3% of patients on benralizumab experiencing an exacerbation compared with 52.0% of patients on placebo over the 28-week treatment period. This was despite the substantial reduction in OCS in the benralizumab group. The use of benralizumab was also associated with improvements in pulmonary function (NSS; pre-bronchodilator FEV_1), ACQ-6 score (indicating better asthma control), and AQLQ(S)+12 score (indicating better asthma-related quality of life) from baseline to week 28.

Results for OCS reductions in European patients were [redacted] with the overall population, with a mean reduction in OCS dose from baseline of [redacted] for patients receiving benralizumab Q8W (n=22) compared with [redacted] for patients receiving placebo (n=23).

Table 21: Primary and key secondary outcomes in the ZONDA trial

	Placebo (N=75)	Benralizumab Q8W (N=73)
Primary outcome		
Median OCS dose (range) – mg/day*		
At baseline	10.0 (7.5 – 40.0)	10.0 (7.5 – 40.0)
At final visit	10.0 (0.0 – 40.0)	5.0 (0.0 – 30.0)
Median reduction from baseline (range) - % of baseline value; p value	25.0 (-150 – 100) -	75.0 (-50 – 100) p<0.001
Reduction from baseline in final OCS dose, n (%)		
≥90%	9 (12)	27 (37)
≥70%	15 (20)	37 (51)
≥50%	28 (37)	48 (66)
>0%	40 (53)	58 (79)
Any increase or no change in dose	35 (47)	15 (21)
Analysis of % reduction from baseline in OCS dose		
Odds ratio (95% CI; p value)	-	4.12 (2.22 – 7.63; p<0.001)
Key secondary outcomes		
Final oral glucocorticoid dose of ≤5 mg/day – n (%)		
Odds ratio (95% CI; p value)	-	2.74 (1.41 – 5.31; p=0.002)
Annual asthma exacerbation rate	1.83	0.54
Rate ratio (95% CI; p value)	-	0.30 (0.17 to 0.53; p<0.001)
Pre-bronchodilator FEV1, LS mean change from baseline (L)	0.126	0.239
LS mean difference	-	0.112 L (95% CI, –0.033 to 0.258; p=0.129)
ACQ-6 score change from baseline	–0.57	–1.12
LS mean difference	-	–0.55 (95% CI, –0.86 to –0.23; P=0.001)
AQLQ score from baseline	0.63	1.08
LS mean difference	-	0.45 (95% CI, 0.14 to 0.76; P=0.004)

* The baseline OCS dose was the daily dose at which the patient's asthma was stabilised at randomisation and the final OCS dose was the final daily dose at week 28.

B.2.7 Subgroup analysis

Based on analysis of the SIROCCO and CALIMA trials, benralizumab was found to be more efficacious in patients with blood eosinophils ≥300 cells/μL and a history of three or more exacerbations in the previous year (compared with patients with lower eosinophil counts and less frequent exacerbations; see page 98). Based on this analysis, and also in-line with clinicians' expectations of the positioning of benralizumab in severe asthma (AstraZeneca 2017), a NICE recommendation is sought in the subgroup of patients with severe eosinophilic asthma inadequately controlled, despite high-dose ICS (≥ 800μg FP daily) plus LABA, with blood eosinophils ≥300 cells per μl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months).

Supporting evidence is based on pooled data from the SIROCCO and CALIMA trials, in patients receiving high-dose ICS (≥ 800μg FP daily) plus LABA, with blood eosinophils ≥300 cells per μl and ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months, as well as a subgroup analysis of patients with blood eosinophils ≥300 cells per μl from the ZONDA trial. These results are described below.

Pooled SIROCCO and CALIMA subgroup analysis

Adult patients with blood eosinophil level ≥300 cells/μl and ≥3 severe exacerbations, who have failed on high-dose ICS plus LABA therapy

A total of 259 patients were included in the pooled SIROCCO and CALIMA subgroup analysis. Pooling increased the sample size and was feasible due to the similar study designs, helping to identify patients who could benefit most from treatment with benralizumab. Overall, 24% of patients were on concomitant OCS and 88% on ICS/LABA, and the median time since asthma diagnosis was 16 years (Table 22). In the 12 months prior to study initiation, patients had experienced a mean of 4.2 exacerbations, with 24% experiencing an exacerbation leading to hospitalisation.

Table 22: Baseline characteristics in the subgroup analysis (pooled SIROCCO and CALIMA)

	Benralizumab 30mg Q8W (N=123)	Placebo (N=136)
Age, mean (SD)	50.8 (11.5)	49.6 (12.7)
Female sex, n (%)	74 (60.2)	93 (68.4)
Race, n (%)		
White	91 (74.0)	106 (77.9)

Black or African American	4 (3.3)	2 (1.5)
Asian	25 (20.3)	21 (15.4)
Other	3 (2.4)	7 (5.1)
Years since asthma diagnosis, median (range)	18.4 (1.3, 66.9)	14.3 (1.2, 69.9)
Pre-bronchodilator FEV_1 (L), mean (SD)	1.60 (0.596)	1.67 (0.632)
Local baseline eosinophil count, mean (SD)	718 (475)	676 (450)
N. exacerbations in past 12 months, mean (SD)	4.0 (1.72)	4.4 (2.32)
N. exacerbations leading to hospitalisation or ER treatment in past 12 months, mean (SD)	0.9 (1.69)	0.9 (1.55)
Patients with ≥1 exacerbations resulting in hospitalisation in past 12 months, n (%)	30 (24.4)	33 (24.3)
Diagnosis of allergic rhinitis, n (%)	77 (62.6)	82 (60.3)
Nasal polyps, n (%)	42 (34.1)	43 (31.6)
History of omalizumab treatment, n (%)	13 (10.6)	16 (11.8)
PRO measures		
Total asthma symptom score	2.84 (1.10)	2.82 (1.01)
ACQ-6 score, mean (SD)	2.87 (0.95)	2.90 (0.92)
AQLQ overall, mean (SD)	3.69 (0.99)	3.87 (0.96)
EQ-5D-5L utility score*	0.73 (0.216)	0.75 (0.181)
Maintenance asthma medication use at baseline		
ICS use, n (%)	123 (100.0)	136 (100.0)
Mean ICS total daily dose (µg)(a)	1236.428	1165.788
LABA use, n (%)	122 (99.2)	136 (100.0)
ICS/LABA use, n (%)	110 (89.4)	117 (86.0)
OCS use, n (%)	29 (23.6)	32 (23.5)
Mean OCS total daily dose (mg)(b)	13.845	12.984
LAMA use, n (%)	20 (16.3)	19 (14.0)
LTRA use, n (%)	62 (50.4)	62 (45.6)
Xanthine derivatives use, n (%)	33 (26.8)	27 (19.9)
Other asthma medications use, n (%)	3 (2.4)	1 (0.7)

(a) ICS doses were converted to their Fluticasone Propionate equivalent for this summary.

(b) OCS doses were converted to their Prednisolone equivalent for this summary.

*UK tariff was used to estimate score

Clinical effectiveness

Using a negative binomial model for assessment, benralizumab was found to significantly reduce the annual asthma exacerbation rate by 53% compared with placebo (RR: 0.47; 95% CI: 0.32 - 0.67; p<0.001) in the pooled subgroup analysis.

Further, benralizumab reduced the rate of exacerbations associated with ER visits by 69% (p=0.051), improved pre-bronchodilator FEV_1 by 254 ml (p<0.001), and improved PRO scores of asthma control and quality of life (ACQ-6 and EQ-5D-5L) from baseline compared with placebo (Table 23). No differences were observed for exacerbations associated with hospitalisation, although event rates were very low.

Table 23: Efficacy in the pooled SIROCCO and CALIMA subgroup analysis

Estimate, 95% CI	Benralizumab 30mg Q8W (N=123)	Placebo (N=136)
Marginal annual exacerbation rate	0.85 (0.63, 1.15)	1.83 (1.45, 2.30)
Marginal absolute difference	-0.98 (-1.46, -0.50)	
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)
Marginal absolute difference	-0.10 (-0.22, 0.01)	
Rate ratio	0.31 (0.09, 1.01)	
P value	0.051	
Annual exacerbation rate associated with hospitalisation	Not calculated*	Not calculated*
Rate ratio	1.01 (0.30, 3.45)	
P value	0.988	
FEV_1 pre-bronchodilator change from baseline (L)	0.485	0.231
Estimate for difference	0.254 (0.113, 0.395)	
P value	<0.001	
ACQ-6 score change from baseline	-1.59	-1.16
Estimate for difference	-0.43 (-0.69, -0.16)	
P value	0.002	
Mean EQ-5D-5L score change from baseline	0.10 (0.08, 0.13)	0.06 (0.04, 0.09)
Estimate for difference	0.04 (0.01, 0.08)	
P value	0.019	

* The crude rate was 0.09 for benralizumab and 0.14 for placebo

ZONDA

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B.2.8 Meta-analysis

Individual patient-level data (IPD) for the key benralizumab exacerbation trials (SIROCCO and CALIMA) were pooled together to inform the MAIC. Direct meta-analysis was not carried out due to this pooling of IPD. Pooled estimates for comparator exacerbation studies (for mepolizumab and reslizumab) were calculated in a meta-analysis performed in Stata statistical software using a drop down command prompt "metan". Fixed-effects estimates were calculated according to the Mantel-Haenszel model, and random-effects estimates according to the method of DerSimonian and Laird.

B.2.9 Indirect and mixed treatment comparisons

Note: this section summarises the methodology and results of the MAIC. For further, more detailed information, please refer to Appendices D.1.1 and D.1.2.

In the absence of head-to-head trials versus mepolizumab and reslizumab, the feasibility of conducting indirect comparisons was assessed.

Search strategy

An SLR was conducted to identify RCT evidence for the efficacy of monoclonal antibodies for severe asthma, in accordance with NICE guidance, and the University of York CRD standards and Cochrane standards. Methods of this systematic review for the identification of relevant benralizumab studies are described in Section B.2.1.

Study selection

The systematic review for indirect and mixed treatment comparisons was conducted with a broader scope than the review for benralizumab RCTs, to incorporate evidence for all relevant comparators in the severe asthma population. Eligibility criteria are described in Table 26.

Table 26: Eligibility criteria (PICOs) for the systematic review

Population	• Age: adults and adolescents (≥12 years) • Gender: any • Race: any • Disease: severe asthma that is uncontrolled despite treatment with medium- to high-dose ICS plus at least one additional controller	
Interventions	• Biologics (in line with the scope of this appraisal) • Benralizumab • Mepolizumab • Reslizumab	
Comparators	• Placebo/best supportive care • Medium or high-dose ICS + at least one additional controller. • Medium dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 2 additional controller (e.g. LABA + LAMA/LABA+LTRA) • High-dose ICS + at least one additional controller + OCS maintenance treatment	
Outcomes of interest	Efficacy and quality of life outcomes: • Asthma exacerbations (overall exacerbations, mean rate per patient per year, exacerbations requiring systemic corticosteroids, ER visit and/or hospitalisation, including definitions) • Number/proportion of patients with exacerbations • Total number of exacerbations experienced over the duration of the study • Time to first exacerbation • Pre-bronchodilator FEV_1 • Post-bronchodilator FEV_1 • Peak expiratory flow • Symptom-free days • Asthma control measured by ACQ • Asthma symptoms (overall, day-time, night-time symptom, night-time awakening) • Oral corticosteroids sparing efficacy • AQLQ or mini AQLQ • SGRQ • EQ-5D • WPAI	
	Safety outcomes: • Any adverse events • Any serious adverse events • Any treatment-related adverse events • Bronchitis • Cardiac events • Cough • Dry mouth	• Hoarseness or dysphonia • Mortality • Nausea • Oral candidiasis • Pneumonia • Palpitations • Sinusitis • Tremor • Upper respiratory tract infections
	Tolerability • All withdrawals • Withdrawal due to adverse events • Withdrawal due to lack of efficacy	
Study designs	• RCTs	

Language	• Database to be searched irrespective of language • English language studies were included in SLR
Publication timeframe	• Database inception to 17 October 2017 • Conference proceedings for past 3 years (searched on 17 October 2017)

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ER: Emergency room; EQ-5D: EuroQoL 5D; FEV_1: Forced expiratory volume in one second; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2 agonist; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene receptor antagonist; RCT: Randomised controlled trial; SGRQ: St. George's Respiratory Questionnaire; SLR: Systematic literature review; WPAI: Work Productivity and Activity Impairment

Identified trials

A total of 2762 separate references were identified through database searching (see Appendix D.1.1 for search terms – **Error! Reference source not found.** to **Error! Reference source not found.**). The search terms included the medicine omalizumab as this was included in the draft scope but was subsequently excluded in the final scope of this appraisal. Hence, omalizumab studies were excluded at the screening phase.

Due to an overlap of evidence across different databases, 470 abstracts were removed as duplicates. Initial screening of the titles and abstracts of the remaining 2,292 citations yielded 390 relevant references, which were evaluated as full-text articles. Of these 390 references, 91 references met the inclusion criteria of the review. In addition, 43 references meeting the inclusion criteria were identified from conference proceedings (n=14), bibliographic screening (n=2), registry databases (n=20), and manufacturers' databases (CSRs, n=7) (see **Error! Reference source not found.** in the appendix for the PRISMA flow). Finally, having linked the multiple publications from each single study, 16 studies from 134 publications were included in the SLR (**Error! Reference source not found.** in the Appendix).

NMA feasibility assessment

The clinical studies identified in the SLR were assessed for potential inclusion in an NMA.

The selection criteria for studies to be assessed for an NMA were based on the proposed label and the patient population for the Phase III of benralizumab, i.e., patients with severe asthma that remained uncontrolled despite treatment with high-dose ICS and at least one additional controller. However, for other biologics approved doses were considered for treatment comparisons. Table 27 details the approved or labelled doses of biologics considered for inclusion of studies for the NMA.

Table 27: Approved interventions and doses in severe asthma

Treatment	Approved/labelled dose
Benralizumab	30 mg Q8W SC (proposed label dose) based on two pivotal trials
Mepolizumab	100 mg Q4W SC; 75 mg IV (bioequivalent to the approved SC dose)
Reslizumab	3 mg/kg Q4W IV

IgE: Immunoglobulin E; IV; Intravenous; Q4W: Every 4 weeks; Q8W: Every 8 weeks; SC: Subcutaneous

As mepolizumab 75 mg IV is considered to be bioequivalent to the approved dose (100 mg Q4W SC), these two doses were pooled in the ITC.

Of the 16 studies included in the SLR, only 10 studies met the criteria for assessment for inclusion in an NMA: three studies each for benralizumab and reslizumab, and four studies for mepolizumab. The feasibility of performing an NMA was assessed in three steps:

- The possibility of constructing an interlinked network of studies
- A comparison of study design and patient demographics that could modify relative treatment effect, and
- The availability of data for each outcome of interest

A heterogeneity assessment was undertaken to evaluate the degree of comparability among the studies that form the evidence network. Based on the heterogeneity assessment across the trials selected for NMA, a high degree of variability was observed in the inclusion/exclusion criteria, baseline characteristics, and disease severity, as assessed by exacerbation history, EOS count, maintenance OCS use, and baseline IgE count of the included patient population. See Appendix D.2 for further details on the heterogeneity assessment.

In the event of cross-trial differences in patient populations and differences in outcome measure definitions, NMA can generate biased estimates. A robust NMA combining all these studies in a single evidence network was therefore not feasible.

Several of the limitations (such as cross-trial differences) that arise based on aggregate data in an NMA can be accounted for using a population-adjusted ITC, wherein individual patient data (IPD) in one or more trials are used to adjust for the cross-trial differences in the distribution of variables that influence the outcomes.

Rationale for MAIC Approach

Matching adjusted indirect comparison (MAIC) is a form of population-adjusted ITC that uses subject-level data from trials of one treatment (in this case for benralizumab using IPD data available to the manufacturer) and matched baseline aggregate data reported in comparator trials (in this case for mepolizumab and reslizumab). Individuals in the IPD population are weighted by the inverse of their propensity score, to balance the covariate distribution with that of target aggregate population. Another type of population-adjusted ITC is Simulated Treatment Comparison (STC) (Phillippo 2016).

The motivation behind using MAIC is to adjust for the cross-trial differences in the patient characteristics and thus generate less biased estimates of effects when compared with standard ITC

Matching-adjusted indirect comparison methodology

In light of the limitations of conducting a standard NMA for comparing benralizumab against other biologics in severe asthma, a MAIC was conducted to assess the relative efficacy across interventions. NICE DSU guidance on the use of MAICs for HTA was used to inform the approach (Phillippo 2016).

Following this guidance, an anchored MAIC method was adopted based on the following rationale:

- Benralizumab and other in-scope biologics (mepolizumab and reslizumab) share a common control group, i.e., placebo, and according to the NICE DSU recommendations only anchored analyses were performed
- MAIC is preferred to simulated treatment comparison (STC) on the basis that it avoids the need to assume a relationship between the effect outcome, e.g., exacerbation rates, and the 'matching' characteristic

The variables selected for adjustment in the MAIC were selected in an ordered way and were also validated with external key opinion leaders (KOLs) (AstraZeneca data on file). The approach included the following steps:

1. Assess whether there existed an effect modifier among the baseline covariates available in both benralizumab and comparator studies and demonstrate that these effect modifiers were distributed differently across the studies included in the MAIC, to justify the use of MAIC
2. Validate the selection with an external clinical KOL
3. Variable adjustment by estimating a logistic propensity score model that was conditional on the effect modifiers identified in the previous steps. The propensity score defined in this context is the conditional probability that an individual in the target population is assigned to the comparator given the covariates. Further, each individual is weighted by the inverse of their propensity score
4. Estimate the relative treatment effects of benralizumab and comparator included in the MAIC using standard ITC methodologies

The results of matched analyses were finally compared with the unmatched results of the ITC to assess the extent to which MAIC had altered the results.

Six key efficacy outcomes were selected on the basis of the primary study endpoint and clinical significance in severe asthma, as well as to inform the economic model:

- Exacerbation trials:

- Annual rate of clinically significant exacerbations (see **Error! Reference source not found.** in Appendix D.1.2 for definition of this outcome in each study included in the MAIC)
- Annual rate of exacerbation requiring emergency room (ER) visit or hospitalisation
- Pre-bronchodilator forced expiratory volume in one second (FEV_1)

- OCS sparing trials:
  - Percentage reduction from baseline OCS dose
  - Proportion of patients with 100% reduction in OCS dose
  - Annual rate of clinically significant exacerbations (See **Error! Reference source not found.** in Appendix D.1.2 for definitions)

Please refer to Appendix D for detailed methodology of the MAIC.

Selection of studies/patient population for MAIC

Only Phase III pivotal trials evaluating approved respiratory biologics in severe uncontrolled asthma on medium to high-dose ICS plus at least one additional controller were considered for inclusion in the MAIC for comparison against benralizumab.

The studies that informed the NMA feasibility assessment were considered for MAIC. The inclusion/exclusion criteria for the SLR were sufficiently broad so as to identify all potentially relevant studies. Further criteria specific to the decision problem were then applied to determine which studies should populate the base case network and sensitivity analyses in the MAIC. All of the SLR criteria as listed in **Error! Reference source not found.** had to be met for data from a study to be used in the MAIC. **Error! Reference source not found.** summarises the criteria for selection of studies for the MAIC.

Table 28: Summary of objectives and eligibility criteria for the MAIC

Objectives	
Objectives	To compare benralizumab against other launched respiratory biologics, i.e., mepolizumab and reslizumab, in patients with severe asthma uncontrolled on high-dose ICS plus LABA (medium- to high-dose ICS plus LABA when compared with reslizumab), and ideally in mepolizumab and reslizumab NICE-recommended populations, respectively
Eligibility criteria	
Population	• Age: adults and adolescents (≥12 years) • Gender: any • Race: any

	• Disease: severe asthma that is uncontrolled despite treatment with high-dose ICS plus at least one additional controller (medium- to high-dose ICS when compared with reslizumab)
Interventions	Approved biologics • Benralizumab • Mepolizumab • Reslizumab Only studies evaluating approved/labelled doses of interventions were included in the MAIC
Comparators	• Placebo/best supportive care • Medium or high-dose ICS + at least one additional controller. • Medium-dose ICS + 1 additional controller (e.g., LABA/LTRA/LAMA/theophylline) • High-dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 2 additional controllers (e.g., LABA + LAMA/LABA+LTRA) • High-dose ICS + at least one additional controller + OCS maintenance treatment
Study designs	• RCTs • Phase III • Phase II trials were not considered for analysis being exploratory in nature and do not provide a definitive answer regarding the clinical benefit of the intervention in question • In addition, studies not powered to detect differences in efficacy outcomes were not considered in the analysis
Language	English language studies
Publication timeframe	Database inception to 17 October 2017 Conference proceedings for past 3 years (searched on 17 October 2017)

ICS: Inhaled corticosteroid; LABA: Long-acting beta-2 agonist; MAIC: Matching-adjusted Indirect Comparison; OCS: oral corticosteroid; RCT: Randomised controlled trial

The following section describes the detailed criteria for selection of studies for the MAIC.

Selection of interventions and dose

Studies evaluating only EMA licensed or US FDA licensed doses of respiratory biologics were included in the MAIC. In studies with multiple treatment arms, active treatment arms that met this criterion were included.

All of the mepolizumab and reslizumab studies included in the SLR qualified the criteria for disease severity. Only Phase III trials were considered to be appropriate for selection in MAIC to give a robust and unbiased comparison. This approach was in-line with other submissions of comparative biologics. Phase II trials were not considered for analysis, being exploratory in nature. The primary aim of Phase II trials is to evaluate if the intervention under investigation demonstrates clinical activity and is well tolerated. These studies do not provide a definitive answer regarding the clinical benefit of the intervention in question.

Apart from the above-listed criteria (**Error! Reference source not found.**), a number of additional factors were also considered for selection of studies for the MAIC against specific comparators (mepolizumab and reslizumab) depending on the comparator trials' population. These included background ICS dose (medium/high) and availability of relevant baseline characteristics for matching. These additional parameters were considered to be essential for selecting studies for MAIC in order to generate a more closely matching sample with the benralizumab trials population. The following sections discuss the additional factors considered for identifying appropriate studies for inclusion in the MAIC, for each comparison.

Sensitivity analyses

The following sensitivity analyses were run. Results can be found in Appendix D.1.2.

- Specifically for the comparison between benralizumab and mepolizumab, there were observed differences between the definitions of high-dose ICS across the benralizumab and mepolizumab trials. In benralizumab trials, high-dose ICS was defined using the GINA guideline definition of >500 µg FP daily or equivalent whereas mepolizumab trials used ≥880 µg FP daily or equivalent criteria to define high-dose ICS. Therefore, each analysis for exacerbation trials was conducted for two high-dose ICS definitions, with one using the mepolizumab study definition of ≥880 µg FP daily or equivalent (considered to be the base case analysis) and the other using benralizumab study definition of >500 µg FP daily or equivalent (applied as a scenario analysis). The mepolizumab study definition of ≥880 µg FP daily or equivalent has been used as the base case for the results reported below as this most closely represents the mepolizumab NICE recommended population. Results for the analysis using the benralizumab study definition of >500 µg FP daily or equivalent are included in Appendix D.1.2 - results of the MAIC.
- Comparison between benralizumab and mepolizumab: Inclusion of MUSCA mepolizumab trial as a sensitivity analysis as this trial was not powered to detect differences in efficacy outcomes
- Exacerbation trials comparison between benralizumab and mepolizumab: The MENSA trial was 32 weeks in duration, considerably different from the duration of the other three studies, i.e., 52 weeks in DREAM, 48 weeks in SIROCCO, and 56 weeks in CALIMA. Therefore, pre-bronchodilator FEV_1 (L) was analysed at 32 weeks (base case), end of the studies (including all four trials), and end of the studies (excluding MENSA).

- Two analyses including base case and sensitivity analyses were conducted for the OCS sparing trials (ZONDA for benralizumab vs SIRIUS for mepolizumab). The base case analysis included EOS count, exacerbation history, OCS dose, BMI, and nasal polyps for matching, while sensitivity analysis included ACQ-5 score and history of omalizumab use in addition to the above variables.
- Percentage reduction in OCS dose: The ZONDA and SIRUS trials varied in terms of study duration. ZONDA was a 28-week study, while SIRIUS was a 24-week study. In order to compare like-for-like, the mean percentage reduction in OCS dose was analysed using 24-week data from both of the trials (base case). To assess the impact of differences in time points, an additional sensitivity analysis was conducted using the end of study data from both the trials, i.e., 28 weeks from the ZONDA trial and 24 weeks from the SIRIUS trial.

Results of the MAIC (base case analysis)

Mepolizumab

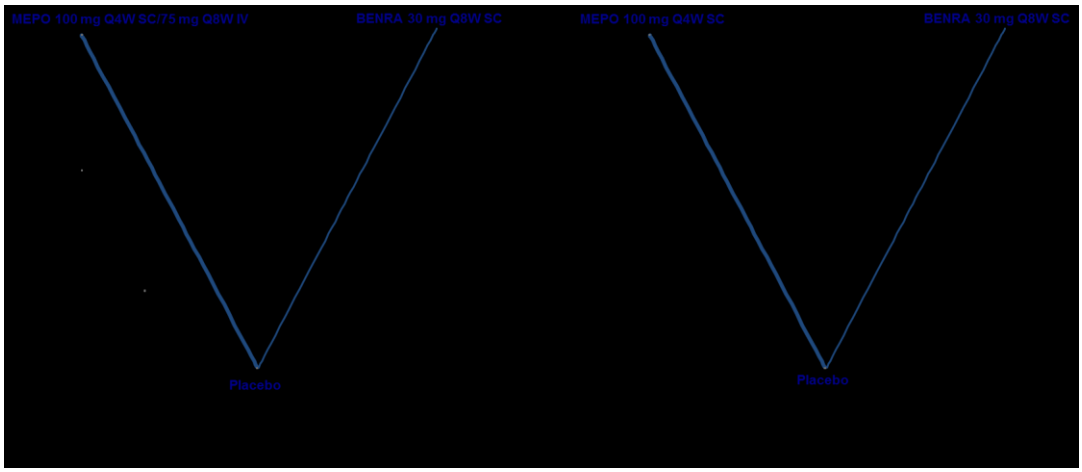
Three studies each for benralizumab, SIROCCO (Bleecker 2016), CALIMA (FitzGerald 2016), and ZONDA (Nair et al. 2017), and mepolizumab, MENSA (Ortega et al. 2014), DREAM (Pavord 2012), and SIRIUS (Bel 2014), met the criteria of approved doses, disease severity, and study phase for inclusion in the MAIC (see **Error! Reference source not found.** in Appendix D.1.2). Additionally, one more trial evaluating mepolizumab was identified, i.e., MUSCA (Chupp et al. 2017). However, the primary objective of MUSCA was to analyse health-related quality of life (HRQoL), and the trial was not powered to detect differences in efficacy outcomes. Moreover, the study duration was comparatively short, i.e., 24 weeks compared with the benralizumab trials (48 weeks in SIROCCO and 56 weeks in CALIMA). MUSCA was therefore not included in the base case, but a sensitivity analysis was conducted including this trial, which is described on page **Error! Bookmark not defined.** in the appendix.

No evidence was found in the mepolizumab NICE-recommended subgroup (EOS ≥300 cells/µl and either 4 exacerbations requiring OCS in the past 12 months or continuous OCS use for the past 6 months). One abstract reporting a post-hoc analysis of the MENSA study in patients with EOS ≥300 cells/µ and ≥3 exacerbations in the prior year was identified, which demonstrated increased efficacy in this subgroup compared with that in the overall MENSA population. However, this analysis was not used for the MAIC as it was only available for one of the two mepolizumab exacerbation trials (i.e., MENSA but not DREAM), and was not conducted in the mepolizumab NICE-recommended population. Please see Appendix D.1.2 – list of identified studies for full details of this abstract.

In order to generate a more matching sample across the studies, background ICS dose was also assessed. Five of the six trials included patients receiving background high-dose ICS. However, the CALIMA trial for benralizumab included patients receiving background medium to high dose ICS. Therefore, only the subgroup of patients receiving high-dose ICS was considered in MAIC. We also assessed studies for data specific to the subgroup of interest to enable a more robust comparison; however limited data were identified, and comparisons were therefore conducted in the overall clinical trial populations.

Figure 21 presents the evidence networks for comparison between benralizumab and mepolizumab across both categories of studies. Treatment differences of each intervention against placebo were used to derive the anchored ITC. For the exacerbation trials, results for benralizumab were obtained by pooling the IPD from the SIROCCO and CALIMA trials, while results for mepolizumab were pooled from the MENSA and DREAM trials. For the OCS sparing trials, SIRIUS and ZONDA were included in the analysis (see Appendix D.1.2 for further details).

Figure 21: Evidence network for comparison of benralizumab vs. mepolizumab for annual rate of clinically significant exacerbations, annual rate of exacerbations leading to ER visit/hospitalisation and change from baseline in pre-bronchodilator FEV1



BENRA: Benralizumab; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q4W: every four weeks; Q8W: every eight weeks; SC: Subcutaneous
Note that benralizumab Q8W dosing included first 3 doses Q4W

Benralizumab and mepolizumab trials varied in terms of baseline EOS count, definition of high-dose ICS, prior history of exacerbation, proportion of patients using OCS at baseline, ACQ-scores, proportion of patients with nasal polyps, and treatment duration (see **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.** in Appendix D.1.2). Nevertheless, the effective sample size (ESS) after adjustment of the trial populations was sufficiently large for a MAIC analysis. Following matching across the exacerbation trials and OCS-sparing trials, benralizumab was compared with mepolizumab for the six key efficacy outcomes. Comparison tables of baseline characteristics of patients before and after matching for each analysis are shown in Appendix D.1.2.

SIROCCO/CALIMA versus MENSA/DREAM (exacerbation trials)

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Reslizumab

A total of six studies assessing reslizumab in severe asthma were identified. Of the included studies, only two studies, Study 3082 (Castro et al. 2015) and Study 3083 (Castro et al. 2015) met the criteria for the MAIC (see **Error! Reference source not found.** in Appendix D.1.1). Since reslizumab studies included patients on medium to high-dose ICS, patients on medium-dose ICS from CALIMA trial (FitzGerald 2016) were also considered for inclusion in MAIC with the aim of improving the matching.

The benralizumab and reslizumab trials varied in terms of sample size, disease severity, medium-dose ICS cut-off, exacerbation history in previous year, and baseline EOS count; there was very low to moderate overlap in the benralizumab and reslizumab trial population in terms of exacerbation history within the past year. High heterogeneity across the baseline characteristics resulted in a considerable reduction in the ESS after adjustments (99% reduction, ESS=20), meaning that a robust MAIC between benralizumab and reslizumab was not feasible. See Appendix D.1.2 – selection of effect modifiers for further details.

One abstract was identified in the reslizumab NICE-recommended population (EOS ≥400 cells/µl and ≥3 exacerbations requiring OCS in the past 12 months), which reported results from a post-hoc, pooled analysis of the two pivotal 52-week trials. Of the 953 patients included in the trials, 158 were included in this analysis, and increased efficacy of reslizumab was found in this subgroup compared with the overall population. These data were not used to assess if a MAIC was possible; however, as baseline characteristics were not reported, and therefore differences between trials could not be adjusted for. Further, the data reported were inconsistent with the data considered to inform the reslizumab NICE recommendation, and the analysis includes a small number of patients. Please see Appendix D.1.2 – list of identified studies for full details of this abstract.

Uncertainties generated by the MAIC

Although the MAIC is associated with several advantages as it uses IPD, the results are still subject to certain limitations.

Firstly, despite balancing the observed patients' characteristics during matching, some unobservable differences may still exist between the trials.

Another limitation is the occurrence of extreme weights for some patients while matching, which can lead to decreased statistical power to detect differences between the treatments. Effective sample size (ESS) is a reliable indicator in such cases. Small ESS can indicate that some patients are receiving extreme weights, and there may be little statistical power to detect differences between treatments. This situation was seen in the sensitivity analysis for the OCS sparing trials (ZONDA vs SIRIUS, with matching for two additional variables, i.e., the proportion of patients with a history of omalizumab use and ACQ-5 scores), wherein the ESS reduced to 44 after matching due to a skewed distribution of weights. As such, results of this sensitivity analysis should be interpreted with caution.

The MAIC methodology tried to address the differences the inclusion or exclusion criteria of the included trials. To account for some of the key differences between trials, additional sensitivity analyses were conducted as described above.

Additionally, across the OCS sparing trials, the studies varied in terms of the eligibility criteria for OCS discontinuation, and the dosing schedule for reduction of OCS. These differences could not be adjusted for using MAIC, so the results of the OCS-sparing trials analyses should be interpreted with caution.

Finally, it should be noted that the MAIC was conducted using ITT data from the trials, as the literature searches found no data for mepolizumab in the subgroup where it is NICE-recommended. We have not identified a reason why the relative effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population (adults with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS and LABA, with ≥300 EOS count, and ≥4 exacerbations in prior year or receiving maintenance OCS). It is therefore deemed a reasonable assumption that the relative treatment effect for benralizumab versus mepolizumab as derived from the MAIC in the full trial populations can be applied to data for the mepolizumab NICE-recommended population, to inform the decision problem in this submission. Further, this was the approach taken in the previous mepolizumab and reslizumab NICE appraisals for comparisons between these medicines and omalizumab.

The results of this analysis have been included in the economic model. (see section B.3.7)

B.2.10 Adverse reactions

Overall rates of AEs in the SIROCCO, CALIMA, and ZONDA ITT analyses

Across all three pivotal trials, the rates of AEs and serious AEs were numerically lower for benralizumab Q8W compared with placebo. Rates of experiencing any AE ranged from 68% to 75% for patients receiving benralizumab across the trials, and from 76% to 83% for patients receiving placebo. Rates of serious AEs ranged from 9% to 13% for benralizumab and from 14% to 19% for placebo.

The most commonly experienced AEs across the trials consistently included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis. Hypersensitivity reactions were infrequent and similar between arms. Relative risk calculations did not indicate an increased risk of any specific AEs when compared between all three trials.

A summary of AEs experienced in SIROCCO, CALIMA, and ZONDA is presented in Table 31, Table 32, and Table 33, respectively, along with absolute and relative risks. Please note that the studies were not powered to detect differences in event rates of AEs, and these calculations are exploratory.

Table 31: Summary of AEs experienced in SIROCCO

	Placebo (n=407)	Benralizumab 30 mg Q8W (n=394)	Risk difference	Relative risk (95% CI)
Any adverse event	311 (76%)	281 (71%)	-5.1%	0.93 (0.86 - 1.01)
Any adverse event leading to treatment discontinuation	3 (<1%)	8 (2%)†	1.3%	2.75 (0.74 - 10.31)
Any serious adverse event	55 (14%)	52 (13%)	-0.3%	0.98 (0.69 - 1.39)
Deaths	2 (1%)	1 (<1%)	-0.2%	0.52 (0.05 - 5.67)
Adverse events in >3% of patients‡				
Asthma	78 (19%)	45 (11%)	-7.7%	0.60 (0.42 - 0.84)
Nasopharyngitis	47 (12%)	46 (12%)	0.1%	1.01 (0.69 - 1.48)
Upper respiratory tract infection	36 (9%)	32 (8%)	-0.7%	0.92 (0.58 - 1.45)
Headache	21 (5%)	37 (9%)	4.2%	1.82 (1.09 - 3.05)
Bronchitis	30 (7%)	19 (5%)	-2.5%	0.65 (0.37 - 1.14)
Sinusitis	28 (7%)	22 (6%)	-1.3%	0.81 (0.47 - 1.39)
Influenza	23 (6%)	19 (5%)	-0.8%	0.85 (0.47 - 1.54)
Pharyngitis	14 (3%)	23 (6%)	2.4%	1.70 (0.89 - 3.25)
Rhinitis	15 (4%)	10 (3%)	-1.1%	0.69 (0.31 - 1.51)
Arthralgia	10 (2%)	18 (5%)	2.1%	1.86 (0.87 - 3.98)
Cough	10 (2%)	13 (3%)	0.8%	1.34 (0.60 - 3.03)

Pyrexia	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Back pain	15 (4%)	8 (2%)	-1.7%	0.55 (0.24 - 1.28)
Acute sinusitis	10 (2%)	13 (3%)	0.8%	1.34 (0.60 - 3.03)
Rhinitis allergic	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Nausea	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Gastroenteritis	6 (1%)	12 (3%)	1.6%	2.07 (0.78 - 5.45)
Pain in extremity	5 (1%)	13 (3%)	2.1%	2.69 (0.97 - 7.46)
Injection-site reactions	8 (2%)	9 (2%)	0.3%	1.16 (0.45 - 2.98)
Hypersensitivity adverse events§	11 (3%)	11 (3%)	0.1%	1.03 (0.45 - 2.36)
Causally related¶	2 (<1%)	2 (<1%)	0	1.03 (0.15 - 7.30)
Urticaria	2 (<1%)	2 (<1%)	0	1.03 (0.15 - 7.30)

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end-of-treatment visit. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

* Includes four patients in the Q8W cohort who received extra doses of benralizumab.

† One additional patient discontinued the study after receiving their last dose but before attending the end-of-treatment visit.

‡ Medical Dictionary for Regulatory Activities version 18.1.

§ High-level term.

¶ In the opinion of the investigator.

Table 32. Summary of AEs experienced in CALIMA

	Placebo (n=440)	Benralizumab 30 mg Q8W (n=428)	Risk difference	Relative risk (95% CI)
Any adverse event	342 (78%)	320 (75%)	-3.0%	0.96 (0.89 - 1.04)
Any drug-related adverse event	36 (8%)	54 (13%)	4.4%	1.54 (1.03 - 2.30)
Any adverse event leading to treatment discontinuation	4 (<1%)	10 (2%)	1.4%	2.57 (0.81 - 8.13)
Any adverse event leading to death	0	2 (<1%)	0.5%	5.14 (0.25 106.75)
Any serious adverse event	60 (14%)	40 (9%)	-4.3%	0.69 (0.47 - 1.00)
Adverse event in >3% of patients*				
Nasopharyngitis	92 (21%)	79 (18%)	-2.6%	0.88 (0.67 - 1.16)
Asthma	68 (15%)	47 (11%)	-4.8%	0.71 (0.50 - 1.01)
Bronchitis	52 (12%)	44 (10%)	-1.6%	0.87 (0.60 - 1.27)
Upper respiratory tract infection	41 (9%)	36 (8%)	-0.9%	0.90 (0.59 - 1.38)
Headache	32 (7%)	34 (8%)	0.8%	1.09 (0.69 - 1.74)
Sinusitis	37 (8%)	20 (5%)	-4.0%	0.56 (0.33 - 0.94)
Influenza	24 (5%)	14 (3%)	-2.3%	0.60 (0.31 - 1.14)
Rhinitis allergic	23 (5%)	16 (4%)	-1.6%	0.72 (0.38 - 1.33)
Hypertension	21 (5%)	18 (4%)	-0.6%	0.88 (0.48 - 1.63)

Rhinitis	17 (4%)	17 (4%)	0.1%	1.03 (0.53 - 1.99)
Back pain	16 (4%)	11 (3%)	-1.1%	0.71 (0.33 - 1.51)
Acute sinusitis	14 (3%)	5 (1%)	-2.2%	0.37 (0.13 - 1.01)
Arthralgia	9 (2%)	14 (3%)	1.3%	1.60 (0.70 - 3.66)
Cough	8 (2%)	14 (3%)	1.6%	1.80 (0.76 - 4.24)
Pharyngitis	7 (2%)	10 (2%)	0.8%	1.47 (0.56 - 3.82)
Pyrexia	6 (1%)	12 (3%)	1.6%	2.06 (0.78 - 5.43)
Injection-site reactions	8 (2%)	9 (2%)	0.3%	1.16 (0.45 - 2.97)
Hypersensitivity	17 (4%)	13 (3%)	-0.9%	0.79 (0.39 - 1.60)
Drug-related hypersensitivity	2 (<1%)	4 (<1%)	0.5%	2.06 (0.38 - 11.17)

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end of therapy visit. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

* Medical Dictionary for Regulatory Activities version 18.1.

Table 33: Summary of AEs experienced in ZONDA

	Placebo (n=75)	Benralizumab 30 mg Q8W (n=73)	Risk difference	Relative risk (95% CI)
Any adverse event	62 (83)	55 (75)	-7.3%	0.91 (0.77 - 1.08)
Any adverse event leading to treatment discontinuation	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Any adverse event leading to death	0	2 (3)	2.7%	5.13 (0.25 - 105.17)
Any serious adverse event	14 (19)	7 (10)	-9.1%	0.51 (0.22 - 1.20)
Adverse event in ≥3% of patients*				
Nasopharyngitis	15 (20)	11 (15)	-4.9%	0.75 (0.37 - 1.53)
Bronchitis	12 (16)	7 (10)	-6.4%	0.60 (0.25 - 1.44)
Headache	4 (5)	6 (8)	2.9%	1.54 (0.45 - 5.24)
Rhinitis	2 (3)	6 (8)	5.6%	3.08 (0.64 - 14.78)
Upper respiratory tract infection	5 (7)	5 (7)	0.2%	1.03 (0.31 - 3.40)
Sinusitis	8 (11)	4 (5)	-5.2%	0.51 (0.16 - 1.63)
Asthma	18 (24)	2 (3)	-21.3%	0.11 (0.03 - 0.47)
Influenza	5 (7)	1 (1)	-5.3%	0.21 (0.02 - 1.72)
Hypertension	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Pneumonia	3 (4)	3 (4)	0.1%	1.03 (0.21 - 4.93)
Vertigo	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Presyncope	0	3 (4)	4.1%	7.19 (0.38 - 136.79)
Back pain	4 (5)	2 (3)	-2.6%	0.51 (0.10 - 2.72)
Cough	4 (5)	1 (1)	-4.0%	0.26 (0.03 - 2.24)
Dyspnoea	4 (5)	1 (1)	-4.0%	0.26 (0.03 - 2.24)

Nausea	3 (4)	0	-4.0%	0.15 (0.01 - 2.79)
Oral candidiasis	4 (5)	0	-5.3%	0.11 (0.01 - 2.09)
Status asthmaticus	3 (4)	0	-4.0%	0.15 (0.01 - 2.79)
Injection-site reaction	2 (3)	0	-2.7%	0.21 (0.01 - 4.21)
Hypersensitivity	1 (1)	2 (3)	1.4%	2.05 (0.19 - 22.17)
Urticaria	1 (1)	1 (1)	0.0%	1.03 (0.07 - 16.12)

Data are number of patients (%).

* Medical Dictionary for Regulatory Activities version 18.1.

Rates of AEs leading to treatment discontinuation were <5% for both benralizumab and placebo across all three trials. Although a numerically higher proportion of patients receiving benralizumab discontinued treatment due to an AE (21 patients receiving benralizumab, compared with 9 patients receiving placebo in total), no trends in specific adverse events leading to discontinuation were observed:

- In SIROCCO, urticaria and arthralgia were the only TEAEs leading to discontinuation of investigational product in more than one patient (2 patients [0.5%] each in the benralizumab 30 mg Q8W group)
- In CALIMA, asthma was the only TEAE leading to discontinuation of investigational product in more than one patient (2 patients [0.5%] in the benralizumab 30 mg Q8W group and 1 patient [0.2%] in the placebo group
- In ZONDA, there were no AEs leading to discontinuation of investigational product in more than one patient

Summary of AEs in the subgroup analysis

In the pooled SIROCCO and CALIMA subgroup analysis (for patients inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl AND ≥3 prior asthma exacerbations), 80.5% of patients who received benralizumab experienced an AE (99/123), compared with 81.6% of patients who received placebo (111/136). The rate of serious AEs was 17.9% in the benralizumab group and 11.8% in the placebo group, while the rate of AEs leading to discontinuation of treatment was 4.1% versus 0.7%, respectively. Serious AEs and discontinuations were examined between the groups and the AEs were spread across many different systems, with no trend for any particular system to be affected. One patient in the benralizumab arm died due to AEs, which was not considered to be study drug-related.

[redacted]

B.2.11 Ongoing studies

Several studies are ongoing to further assess the efficacy and safety of benralizumab in patients with severe asthma. These are summarised in Table 34.

Table 34. Overview of relevant ongoing Phase 3 clinical trials of benralizumab for severe uncontrolled asthma

Phase 3 trial (clinical trial #, status)	Aim	Study design [Location, Year]	Population (N)	Treatment (duration)	Primary and key secondary endpoints
BORA (D3250C00021, NCT02258542)	Study to demonstrate the long-term safety of benralizumab (extension of SIROCCO, CALIMA & ZONDA)	Randomised, Double-blind, Parallel Group, Extension Study [countries see SIROCCO, CALIMA, and ZONDA; 2014-ongoing]	Adult and adolescent patients 12-75 years of age who completed the double-blind treatment period in a predecessor study on benralizumab or matching placebo (N=1800-2000 up to a max of 2200).	30 mg subcutaneous injection for up to 72 weeks of either: Benralizumab Q4W Benralizumab Q8W	Primary endpoint: Safety & tolerability Secondary: • Annual asthma exacerbation rate • HCRU and productivity loss (WPAI+CIQ) • Pulmonary function • Asthma control (ACQ-6) • QoL (AQLQ(S)+12, EQ-5D)
MELTEMI (D3250C00037 NCT02808819)	Study to continue to characterize the safety profile of benralizumab administration and monitor the pharmacodynamic activity of the drug in those asthma patients who remain on treatment for at least 16 weeks and not more than 40 weeks in the predecessor study D3250C00021 (BORA).	Open-label, parallel group, extension study [countries see BORA; 2016 – ongoing]	See BORA (N=770)	30 mg subcutaneous injection of either: Benralizumab Q4W Benralizumab Q8W	Primary: Safety & tolerability Secondary: • Annual asthma exacerbation rate • Absolute eosinophil count • Anti-drug antibody

D3250C00031 (GRECO) (NCT02918071)	Study to assess functionality, performance and reliability of a single-use AI with benralizumab administered subcutaneously in an at-home setting reported by the patient/caregiver, and to confirm the safety, clinical benefit of benralizumab in severe asthma patients	Multicentre, Open Label, Single Group [US, Canada; 2016]	18-75 years with severe not well-controlled asthma, currently treated with ICS/LABA with/without additional asthma controller(s) and having a history of 1 or more asthma exacerbation (N=120)	30 mg subcutaneous injection Q4W (5 injections in total) for up to 28 weeks assessment	Primary: Proportion of • Successful administration • Functional AI • Product complaints Secondary: • Asthma control (ACQ-6) • Pharmacokinetics • Safety
ANDHI (NCT03170271)	Study to investigate the effect of benralizumab on the rate of asthma exacerbations, patient reported quality of life and lung function during 24-week treatment in patients with uncontrolled, severe asthma with eosinophilic inflammation	Multicentre, randomised, double-blind, parallel assignment	18-75 years with severe uncontrolled asthma, currently treated with ICS/LABA and having a history of ≥2 exacerbations	30 mg subcutaneous injection on day 0, 28, 56, and 112	Primary: Effect of benralizumab on the rate of asthma exacerbations Secondary: SGRQ change from baseline
SOLANA (NCT02869438)	Study to evaluate the onset of effect and time course of change in lung function with benralizumab in severe, uncontrolled asthma patients with eosinophilic inflammation	Multicentre, randomised, double-blind, parallel assignment	18-75 years with severe uncontrolled eosinophilic asthma (≥300 cells/µl) and a history of ≥2 exacerbations	30 mg subcutaneous injection on day 0, 28, and 56	Primary: effect of benralizumab on the time course of change on lung function Secondary: FEV1, blood eosinophils, ACQ-6, SGRQ, nitric oxide, lung function metrics

ACQ-6 Asthma control questionnaire 6; AI Auto-injector; APFS Accessorised pre-filled syringe; AQLQ(S)+1 Standardised Asthma Quality of Life Questionnaire for patients 12 years and older; EU European Union; EQ-5D-5L EuroQol-5 Dimensions 5-Level; FDA Food and Drug Administration; FEV_1 Forced expiratory volume in 1 second; HCRU Healthcare resource utilisation; ICS Inhaled corticosteroid; LABA Long-acting β_2 agonist; OCS Oral corticosteroid; PEF Peak expiratory flow; Q4W Once every 4 weeks; Q8W Once every 8 weeks; QoL Quality of life; UK United Kingdom; US United States; WPAI+CIQ Work Productivity and Activity Impairment + Classroom Impairment Questions.

B.2.12 Innovation

Benralizumab has an innovative and unique mechanism of action. By binding to eosinophils through IL-5Rα, benralizumab blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil. Additionally, due to an afucosylated section on the molecule itself, benralizumab increases the affinity of eosinophils to Natural Killer (NK) cells. This leads to a rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in a systemic efficacy response (Laviolette et al. 2013). Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84 (Laviolette et al. 2013).

In contrast, mepolizumab and reslizumab act by binding to IL-5 and inhibiting IL-5 signalling, thereby indirectly reducing the activation, proliferation, and survival of eosinophils (Figure 1) – this ultimately results in eosinophil reduction but not depletion.

Currently, benralizumab is the only anti eosinophilic treatment available for administration through an accessorised prefilled syringe (APFS) and convenient every 8-week dosing for SC injection, reducing the number of product administration visits and associated administration costs, and facilitating home administration by a HCP, where needed. In comparison, reslizumab and mepolizumab require reconstitution before administration with associated resource use: reslizumab is administered by IV infusion every 4 weeks and dosing is weight-dependent; mepolizumab is administered SC every 4 weeks (EMA 2016, AstraZeneca 2017, EMA 2017).

B.2.13 Interpretation of clinical effectiveness and safety evidence

Overview

The key evidence to support the effectiveness of benralizumab in severe asthma is based on three pivotal Phase 3 placebo-controlled clinical trials (SIROCCO, CALIMA, and ZONDA), and a matched-adjusted indirect comparison (MAIC) against mepolizumab.

Interpretation of subgroup evidence versus SOC for the population in which a NICE recommendation is sought *(severe eosinophilic asthma inadequately controlled, despite high-dose ICS plus LABA, with blood eosinophils ≥300 cells/µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months)*

Throughout the Phase 3 clinical trial programme, benralizumab demonstrated statistically significant reductions in the annual exacerbation rate compared with placebo in the overall ITT analyses, when both were added to standard of care therapy. The similar trial designs of SIROCCO and CALIMA allowed the results to be pooled, to better understand the relationship between the clinical efficacy of benralizumab and characteristics such as baseline blood eosinophil counts and exacerbation history, and therefore identify which patients are most likely to benefit from treatment with benralizumab.

Annual exacerbation rate

Based on the results of the pooled analysis, benralizumab was found to be more efficacious in patients with blood eosinophils ≥300 cells/μL and a history of three or more exacerbations in the previous year (compared with patients with lower eosinophil counts and less frequent exacerbations). This subgroup also reflected clinical experts' expectations of where benralizumab is likely to provide the most benefit (AstraZeneca 2017). In these patients, benralizumab was found to significantly reduce the annual asthma exacerbation rate by 53% compared with placebo (RR: 0.47; 95% CI: 0.32 - 0.67; p<0.001) (AstraZeneca data on file 2017).

In the subgroup of ZONDA patients with blood eosinophils ≥300 cells/μl, benralizumab reduced the annual exacerbation rate by [redacted]

Exacerbations leading to hospitalisation

In the pooled SIROCCO and CALIMA subgroup analysis (patients with blood eosinophils ≥300 cells/μL and ≥3 exacerbations in the previous year), benralizumab reduced the annual exacerbation rate associated with ER visits by 69%, though this did not reach statistical significance (RR: 0.31; 95% CI: 0.09, 1.01; p=0.051). There was no difference in the annual exacerbation rate associated with hospitalisation, due to low event rates.

In the subgroup of ZONDA patients with blood eosinophils ≥300 cells/μl, [redacted]

Exacerbations associated with severe, uncontrolled eosinophilic asthma are associated with a considerable clinical, humanistic, and economic burden. For example, total mean healthcare resource use and associated costs for patients with severe uncontrolled eosinophilic asthma have been estimated to be 4 times higher than in the overall asthmatic population. Therefore, reductions in exacerbation rates with benralizumab in the subgroup where a NICE recommendation is sought could lead to improved patient outcomes, including lower mortality (as assumed in the model), and decreased NHS resource use.

OCS dose reductions

In the OCS-sparing ZONDA trial, in the subgroup of patients with blood eosinophils ≥300 cells/µl, benralizumab reduced the median final OCS dose by [redacted]

Reductions in OCS dose represent an important goal in severe, uncontrolled eosinophilic asthma due to the need to mitigate OCS-associated complication risks such as obesity, diabetes, osteoporosis, and peptic ulcerations. These complications are dose-exposure dependent and are associated with high costs – for example, patients on maintenance OCS incur 43% higher estimated costs than those not on maintenance OCS. Benralizumab could therefore provide patients with an important new OCS-sparing option, that reduces the clinical and economic burden associated with OCS use.

Quality of life

Benralizumab was also associated with improvements in quality of life measures from baseline. For example, in the pooled SIROCCO and CALIMA subgroup analysis (patients with blood eosinophils ≥300 cells/µL and ≥3 exacerbations in the previous year), the mean EQ-5D score change from baseline was 0.10 for benralizumab compared with 0.06 for placebo (estimate for difference of 0.04; 95% CI: 0.01, 0.08; p=0.019). In the subgroup of ZONDA patients with blood eosinophils ≥300 cells/µl, the AQLQ(S)+12 score change from baseline was [redacted]

Interpretation of MAIC results versus mepolizumab

In the absence of head-to-head trials against the key comparators mepolizumab and reslizumab, the feasibility of conducting an indirect comparison was assessed. Based on heterogeneity assessment, cross-trial differences were too large to conduct a robust NMA combining relevant trials between benralizumab and these comparators. A population-adjusted ITC approach, specifically MAIC, was therefore considered to adjust for cross-trial differences and assess comparative efficacy. The approach followed the NICE DSU guidance on the use of MAICs in HTA.

Despite between-trial differences between benralizumab and mepolizumab, the ESS after adjustment of the trial populations was sufficiently large for a robust MAIC analysis. Two networks were constructed: one for exacerbation trials (SIROCCO/CALIMA for benralizumab and MENSA/DREAM for mepolizumab), and one for OCS sparing trials (ZONDA for benralizumab and SIRIUS for mepolizumab).

Following matching and adjustment for differences, [redacted]

Generalisability of the MAIC to the subgroup of interest should be considered when interpreting these results, as the analysis was conducted in the overall population, and then applied to the benralizumab subgroup data for which mepolizumab has a NICE recommendation (i.e., patients with ≥300 eosinophils and ≥4 exacerbations in the past year).

For the comparison between benralizumab and reslizumab, high heterogeneity across the baseline characteristics resulted in a considerable reduction in the ESS after adjustments (99% reduction, ESS=20), meaning that a robust MAIC was not feasible.

Interpretation of the safety data

In terms of safety outcomes, benralizumab was found to be well tolerated, with rates of AEs, serious AEs, and AEs leading to discontinuation of treatment being similar between benralizumab and placebo. Most AEs were mild to moderate in intensity, and not considered to be related to treatment. The most commonly experienced AEs across the trials consistently included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis. Although small numerical differences in incidences were observed across groups for some of the most common TEAEs, none of these differences were considered to be clinically meaningful. No deaths were considered to be related to treatment.

Study durations ranged from 28 weeks (ZONDA) to 48 weeks (SIROCCO), to 56 weeks (CALIMA), and longer-term data needed to confirm the persistence of treatment effect are not currently available. The ongoing BORA and MELTEMI extension trials are designed to evaluate long-term efficacy and safety with benralizumab (Section B.2.11).

End of life criteria were not considered in this appraisal.

B.3 Cost effectiveness

Summary of key points

- A *de novo* Markov model was developed to assess the cost-effectiveness of benralizumab compared with SoC in the base case population (severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with mOCS over the previous 6 months) and with mepolizumab and reslizumab in their respective NICE recommended populations.
- The ICER for add-on benralizumab (+PAS) compared with SoC alone was £34,284/QALY gained in the base case population, with benralizumab providing an additional [redacted] QALYs at an additional cost of £[redacted] per-patient
- As the comparators have a confidential PAS, ICERs were calculated using the net price of benralizumab and the list prices of mepolizumab and reslizumab. Results of this analysis showed that benralizumab was dominant versus both comparators (using benralizumab PAS price versus comparator list price):
    - Mepolizumab: [redacted] incremental QALYs; £[redacted] savings (in the mepolizumab NICE-recommended population)
    - Reslizumab: [redacted] QALYs; £[redacted] savings. (in the reslizumab-NICE recommended population)
    - Sensitivity analysis is provided exploring different levels of PAS discount for mepolizumab and reslizumab

B.3.1 Published cost-effectiveness studies

A systematic literature review was undertaken to identify cost-effectiveness studies relevant to the Decision Problem. The eligibility criteria implemented is provided in Table 35 and search strategy details are provided in Appendix G. The search was undertaken on 6th November 2017. The search was undertaken according to NICE requirements (NICE 2013).

Table 35: Eligibility criteria for the Systematic Review

Criteria	Inclusion criteria
Population	Adults, children and young people aged ≥12 years with severe asthma Disease severity classified according to validated criteria (e.g. the Global Initiative for Asthma [GINA] criteria)
Intervention	• Benralizumab • Reslizumab • Mepolizumab

	• Omalizumab No restriction on dose or duration of treatment or use of concomitant best supportive care
Outcomes	Main outcomes, to include: • Incremental costs-effectiveness ratio (ICER): Cost per quality-adjusted life year (QALY) • ICER: Cost per disability-adjusted life year (DALY) • ICER: Cost per event avoided Additional outcomes: • Range of ICERs as per sensitivity analyses • Assumptions underpinning model structures • Key costs drivers • Sources of clinical, cost and quality of life inputs • Discounting of costs and health outcomes • Model summary and structure
Study design	• Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses
Territory of interest	No restriction
Date of publication	2012 onwards
Language of publication	English language publications or foreign language publications with an English abstract

Description of identified studies

The relevant studies identified through the cost-effectiveness SLR are summarised in Table 36 below.

Table 36: Summary list of published cost-effectiveness studies

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
Dal Negro 2012 (Dal Negro et al. 2012) Italy	Pre-post comparison of patients from an institutional database¶ Time horizon, 12 months prior to and 36 months after the initiation of omalizumab Perspective, Payer Cycle length, NA Discounting costs/benefits: NA	1-year pre-omalizumab 36 months post-omalizumab	Patients with severe, persistent atopic asthma as per Global Initiative for Asthma (GINA) guideline definition, resistant to daily high-dose anti-asthma drugs with add-on omalizumab for ≥36 months • Mean age (min, max), 45.4 years (31, 64) • Female gender, 50%	**Mean total costs per patient (SD) [€, 2011]** • Pre-omalizumab, €2,869 (1,383) • Post-omalizumab, €8,038 (2,096)	**Mean (SD) per patient** *FEV1 (% predicted)* • Pre-omalizumab, 57 (12) • Post-omalizumab, 76 (19) *ACT (score)* • Pre-omalizumab, 11.56 (3.22) • Post-omalizumab, 19.91 (4.12) *Exacerbations (n/year)* • Pre-omalizumab, 2.06 (1.12) • Post-omalizumab, 0.94 (0.46) *Inactivity (days/year)* • Pre-omalizumab, 19 (21) • Post-omalizumab, 76 0 (0)	**ICER [cost/ QALY]** Omalizumab add-on therapy, €23,880

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
					Utility increment (SD), 0.22 (0.16)	
del Carmen Vennera 2016 (del Carmen Vennera et al. 2016) Spain	Pre-post comparison of patients from a specialised asthma unit Time horizon, 12 months prior to and 12 months after the initiation of omalizumab Perspective, Societal Cycle length, NA Discounting costs/benefits: NA	Pre-omalizumab (standard therapy for ≥12 months) Post-omalizumab (≥12 months)	Patients ≥17 years (n=86) with severe persistent allergic asthma uncontrolled by standard treatment for ≥12 months receiving omalizumab for ≥12 months in the Pulmonary and Respiratory Allergy Service, Hospital Clinic de Barcelona, Spain from January 2005 to April 2014 • Mean age (SD), 50.57 years (13.63) • Female gender, 59.2%	**Mean annual total costs per patient (95% CI) [€, 2016]** • Pre-omalizumab, €8,052.34 (7,122.11, 8,974.53) • Post-omalizumab, €16,783.15 (15,236.14, 18,602.70)	**Mean (SD) exacerbation rate (with/without ER visit or hospital admission)** • Pre-omalizumab, 10.77 (5.94) • Post-omalizumab, 3.05 (4.12) **Mean (SD) Asthma Control Test (ACT) score†††** • Pre-omalizumab, 13.61 (4.71) • Post-omalizumab, 19.96 (4.31)	**ICER (95% CI) Cost/exacerbation avoided** *Direct costs only* Omalizumab add-on therapy, €1,487.46 (1,241.21, 1,778.34) *Total costs* Omalizumab add-on therapy, €1,130.93 (909.08, 1,392.86) ***Cost/3-point increase of the ACT score*** *Direct costs only* Omalizumab add-on therapy, €5,425.13 (4,539.30, 6,551.03) *Total costs* Omalizumab add-on therapy, €4,124.79 (3,281.69, 5,186.73)

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
Levy 2015 (Levy et al. 2015) Spain	Pre-post comparison of patients attending an asthma unit Time horizon, 10 months prior to and 10 months after the initiation of omalizumab Perspective, Payer (Spanish NHS) Cycle length, NA Discounting costs/benefits: NA	10 months pre-omalizumab 10 months post-omalizumab	Patients (n=79) aged >14 years diagnosed with severe persistent asthma not controlled after >1 year of follow up attending the Severe Asthma Unit, Pneumology Service, Hospital Universitario Virgen de la Victoria (HUVV), Malaga between July 2008 and July 2012. • Mean (SD) age, 54 years (12.67) • Female, 77.9% Severe, persistent asthma diagnosed according to Spanish Guidelines for Asthma Management (GEMA 2009)	**Mean costs per patient (95% CI) [€, 2012]** • Pre-omalizumab, €1,850 78 (1,519.46, 2,182.10) • Post-omalizumab, €5,431.87 (4,930.72, 5,933.02)	**Total QALYs (95% CI)** • Pre-omalizumab, 0.4972 (0.4768, 0.5177) • Post-omalizumab, 0.6305 (0.6027, 0.6584)	**ICER (95% CI)** ***C**ost/QALY* Omalizumab add-on therapy, €26,864 (21,632.07, 33,859.49) ***C**ost/exacerbation avoided* Omalizumab add-on therapy, €462.08 (347.65, 606.22)
Morishima 2013 (Morishima et al. 2013) Japan	Markov model Time horizon, lifetime‡ Perspective, Societal	Omalizumab + standard therapy Placebo + standard therapy	Patients with severe asthma • Mean age, 50 years • Male gender, 50%	**Mean lifetime discounted costs (95% CI) [$, 2010]** • Omalizumab, $114,100 (114,000, 114,200) • Standard therapy, £43,000	**Total QALYs (95% CI) [discounted]** • Omalizumab, 16.10 (16.05, 16.12) • Standard therapy, 16.00	**ICER (95% CI) [cost/QALY]** • Omalizumab vs standard therapy, $755,200 (614,200-1,298,500) • Responder subgroup§ vs

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	Cycle length, 1 week Discounting costs: 3.0% Discounting benefits: 3.0% Health states • Symptom-free asthma • Day-to-day asthma • Asthma-related exacerbations† • Death			• Responder subgroup§, $155,300 (155,300, 155,300)	• Responder subgroup§, 16.19 (16.14, 16.26)	standard therapy, $590,100 (430,700-858,600)
Norman 2013 (Norman et al. 2013) [This analysis formed part of the NICE MTA appraisal of omalizumab (TA278] Faria 2014 (Faria et al. 2014) [Analysis by Faria considered cost-effectiveness under the PAS discounted price] UK	Markov model Time horizon, lifetime (age 100 years) Perspective, Payer (UK NHS) Cycle length, 3 months Discounting costs: 3.5%	Omalizumab add-on therapy to optimised standard step 4 or 5 GINA therapy Standard step 4 or 5 GINA therapy	Patients uncontrolled at step 4, and in the process of moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy	**Mean costs [£, 2010]** ***List price analysis (Norman 2013)*** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, £72,938 • Standard therapy, £33,218 *Children (6-11 years): age at model entry, 9 years*	**Mean QALY** ***List price analysis (Norman 2013)*** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, 14.13 • Standard therapy, 13.66 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, 17.39	**ICER [cost/QALY]** ***List price analysis (Norman 2013)*** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab vs standard therapy, £83,822 *Children (6-11 years): age at model entry, 9 years*

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	Discounting benefits: 3.5% Health states • Day-to-day asthma symptoms ± omalizumab • Asthma death • Other cause death • Clinically significant severe exacerbation • Clinically significant non-severe exacerbation			• Omalizumab, £92,497 • Standard therapy, £40,218 ***PAS analysis (Faria 2014)*** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, £60,406 • Standard therapy, £33,153 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, £76,386 • Standard therapy, £40,575	• Standard therapy, 16.72 ***PAS analysis (Faria 2014)*** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab, 14.14 • Standard therapy, 13.66 *Children (6-11 years): age at model entry, 9 years* • Omalizumab, 17.39 • Standard therapy, 16.72	• Omalizumab vs standard therapy, £78,009 ***PAS analysis (Faria 2014)*** *Overall population* • ≥ 12 years, £57,557 • 6-11 years, £53,348 *Hospitalisation subgroup* • ≥ 12 years, £31,782 • 6-11 years, £30,109 *Maintenance OCS subgroup* • ≥ 12 years, £34,386 *≥3 exacerbations* • ≥ 12 years, £53,087 • 6-11 years, £48,537
Suzuki 2017 (Suzuki et al. 2017) Brazil	Markov model‡‡ Time horizon, lifetime	Omalizumab add on to standard therapy Standard therapy (ICS + LABA + rescue	Patients with uncontrolled, severe allergic asthma (n=416)	**Total costs [Brazilian Real (R$), 2015]** • Omalizumab, R$295,740	**QALY** • Omalizumab, 10.84 • Standard therapy, 5.64	**ICER [cost/QALY]** • Omalizumab vs standard therapy, R$53,890

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	Perspective, Payer (public healthcare) Cycle length, 3 months Discounting costs: 5.0% Discounting benefits: 5.0% Health states • Day-to-day asthma symptoms with omalizumab add-on therapy • Day-to-day asthma symptoms with standard therapy • Clinically significant non-severe exacerbation • Clinically significant severe exacerbation • Death from all causes • Asthma-related death	medication [OCS and SABA])	*Age* • <12 years, 0.5% • 12-17 years, 5.0% • 18-64 years, 88.0% • >65 years, 6.5% • Female, 35.3%	• Standard therapy, R$15,340		

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
van Nooten 2013 (van Nooten et al. 2013) Netherlands	Markov model‡‡ Time horizon, lifetime (from age 40) Perspective, Societal Cycle length, NR (assumed to be 3 months) Discounting costs: 4.0% Discounting benefits: 1.5% Health states • Daily symptoms (may experience bon-clinically significant exacerbations) • Clinically significant state • Clinically significant severe state • Death from all causes	Omalizumab add on to standard therapy Standard therapy	Patients (≥12 years) with uncontrolled allergic (IgE mediated) asthma despite treatment with high dose ICS (>1000 µg) beclomethasone) and a LABA enrolled in the eXpeRience registry	**Total lifetime costs [€, 2010]** *Undiscounted* • Omalizumab, €227,688 • Standard therapy, €161,499 *Discounted* • Omalizumab, €151,619 • Standard therapy, €95,754	**QALY** *Undiscounted* • Omalizumab, 15.98 • Standard therapy, 14.26 *Discounted* • Omalizumab, 12.86 • Standard therapy, 11.40 **LY** *Undiscounted* • Omalizumab, 25.74 • Standard therapy, 23.93 *Discounted* • Omalizumab, 25.74 • Standard therapy, 23.93	**ICER** **Cost/QALY** *Undiscounted* • Omalizumab vs standard therapy, €38,528 *Discounted* • Omalizumab vs standard therapy, €38.371 **Cost/LY** *Undiscounted* • Omalizumab vs standard therapy, €36,418 *Discounted* • Omalizumab vs standard therapy, €30,738

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	• Death due to clinically significant severe exacerbations					
Whittington 2017 (Whittington et al. 2017) US	Markov model Time horizon, Lifetime Perspective, Payer Cycle length, 2 weeks Discounting costs: 3.0% Discounting benefits: 3.0% Health states • Day-to-day asthma symptoms (i.e. non-exacerbation) • Asthma-related event requiring OCS burst • Asthma-related ER visit • Asthma-related hospitalisation	Mepolizumab add on to standard therapy Standard therapy	Patients with severe, uncontrolled asthma with evidence of eosinophilia • Mean age, 50 years • Female, 57%	**Lifetime costs [$, 2014]** *Treatment cost* • Mepolizumab, $706,111 • Standard therapy, $98,083 *Non-treatment cost* • Mepolizumab, $15,465 • Standard therapy, $33,552	**Lifetime QALY** • Mepolizumab, 15.12 • Standard therapy, 13.569	**ICER** **Cost/QALY** • Mepolizumab vs standard therapy, $385,546 **Cost/ exacerbation avoided** • Mepolizumab vs standard therapy, $24,626

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	• Death (includes mortality related to asthma exacerbation, general disease course, and other all-cause mortality)					
Zafari 2016 (Zafari et al. 2016) US	Markov model Time horizon, 5 years†† Perspective, Payer Cycle length, 1 week Discounting costs: 3.0% Discounting benefits: 3.0% Health states • Exacerbation free • Exacerbation requiring OCS • Exacerbation requiring ER visit	Omalizumab Bronchial thermoplasty (BT) Standard step 3 or 4 GINA therapy	Adults aged 18-65 years (mean age 40 years) with moderate-to-severe allergic asthma who were uncontrolled despite using high dose ICS or ICS + LABA	**Five-year mean discounted costs (95% CI) [$, 2013]** • Standard therapy, $15,400 (14,700, 16,300) • BT, $28,100 (27,600, 29,100) • Omalizumab, $117,000 (116,000, 118,000)	**Five-year QALYs (95% CI) [$, 2013]** • Standard therapy, 3.08 (1.64, 4.21) • BT, 3.24 (1.78, 4.38) • Omalizumab, 3.26 (1.80, 4.40)	**ICER [cost/QALY]** • BT vs standard therapy, $78,000 • Omalizumab vs standard therapy, $552,000 • Omalizumab vs BT, $3,86 million

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	• Exacerbation requiring hospitalisation • Death					
CADTH CDR Mepolizumab 2015 (Canadian Agency for Drugs & Technologies 2016)	Markov Time horizon, lifetime Perspective, Payer Cycle length, 4 weeks Discounting costs: 5.0% Discounting benefits: 5.0% Health states • Day-to-day asthma symptoms for patients receiving a biologic • Day-to-day symptoms for patients receiving standard therapy • Asthma-related mortality • All-cause mortality	Mepolizumab add-on to standard therapy Omalizumab add-on to standard therapy Standard therapy	Adult patients with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) with symptoms inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s), and who have experienced ≥ 2 exacerbation in the past year or who have dependency on systemic corticosteroids	**Total costs [CAN$, 2015]** • Mepolizumab, CAN$167,100 • Omalizumab, CAN$232,293 • Standard therapy, $42,258	**QALY** • Mepolizumab, 11.09 • Omalizumab, 10.86 • Standard therapy, 10.22 **Exacerbations** • Mepolizumab, 15.02 • Omalizumab, 17.72 • Standard therapy, 20.56 **Life-years** • Mepolizumab, 14.59 • Omalizumab, 14.32 • Standard therapy, 14.08	**ICER** ***Manufacturer submission*** **Cost/QALY** • Mepolizumab vs standard therapy, CAN$143,778 • Mepolizumab vs omalizumab, dominant **Cost/ exacerbation avoided** • Mepolizumab vs standard therapy, CAN$22,540 • Mepolizumab vs omalizumab, dominant ***CDR reanalysis*** **Cost/QALY** • Mepolizumab vs standard therapy, CAN$521,838

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
						• Mepolizumab vs omalizumab, cost saving
CADTH CDR Reslizumab 2017 (Canadian Agency for Drugs & Technologies 2017)	Decision tree/Markov (CMA also conducted to compare reslizumab with omalizumab and mepolizumab) Time horizon, lifetime Perspective, Payer Cycle length, 2 weeks Discounting costs: 5.0% Discounting benefits: 5.0% Health states • Day-to-day asthma • Hospitalisation for asthma exacerbation • ER for asthma exacerbation	Reslizumab add-on to standard therapy Standard therapy	Patients with inadequately controlled severe eosinophilic asthma inadequately controlled with medium-to-high dose ICS and an additional asthma controller(s) (e.g. LABA) and blood eosinophil count of ≥400 cells/µl	**Total costs [CAN$, 2015]** • Reslizumab, CAN$139,058 • Standard therapy, CAN$32,650	**QALY** • Reslizumab, 4.421 • Standard therapy, 4.005	**ICER [cost/QALY]** ***Manufacturer submission*** • Reslizumab vs standard therapy, CAN$256,090 [CMA reported reslizumab to be cost saving vs mepolizumab and omalizumab (CAN$2,174 to CAN$3,107/ year)] ***CDR reanalysis*** • Reslizumab vs standard therapy, CAN$888,657

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	• OCS for asthma exacerbation • Unscheduled GP visit for asthma exacerbation • Death from asthma • Death for other causes					[CMA reported reslizumab to be cost saving vs mepolizumab (CAN$1,491/ year) and associated with an incremental cost vs omalizumab (CAN$4,655/ year)]
NICE TA278 2013 (NICE 2013) MTA review of TA133 and TA201‡‡‡ Results of the ERG model are reported in Norman 2013 (Norman et al. 2013) UK	Markov model Time horizon, Lifetime Perspective, Payer Cycle length • First cycle, 16 weeks • Second cycle (children), 8 weeks • Second cycle (aged ≥12 weeks), 10 weeks, subsequent cycles 3 months Discounting costs: 3.5% Discounting benefits: 3.5%	Omalizumab add-on to standard therapy Standard therapy	Patients with severe persistent allergic asthma uncontrolled despite daily high-dose ICS plus a LABA at BTS/SIGN step 4 or 5. Two base case populations considered (i) adults plus adolescents aged ≥12 years; (ii) children aged 6 to 11 years	**Incremental costs [£, 2010]** *Adults/adolescents (≥ 12 years)* • Omalizumab vs standard therapy, £40,748 *Children (6-11 years): age at model entry, 9 years* • Omalizumab vs standard therapy, £54,432	**Incremental QALY** *Adults/adolescents (≥ 12 years)* • Omalizumab vs standard therapy, 1.27 *Children (6-11 years): age at model entry, 9 years* • Omalizumab vs standard therapy, 0.67	**ICER [cost/QALY]** *Adults/adolescents (≥ 12 years): age at model entry, 43 years* • Omalizumab vs standard therapy, £32,076 *Children (6-11 years): age at model entry, 9 years* • Omalizumab vs standard therapy, £80,747

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	Health states • Day-to-day symptoms; standard therapy • Day-to-day symptoms; omalizumab responders • Clinically significant exacerbation • Clinically significant, severe exacerbation • All-cause mortality • Asthma-related mortality					
NICE TA431 2017 (NICE 2017) SMC 1149/16 (Scottish Medicines Consortium 2016) [A summary of the ERG response and additional analysis undertaken is provided in Bermejo 2017 (Bermejo et al. 2017)	Markov model Time horizon, Lifetime Perspective, Payer Cycle length, 4 weeks Discounting costs: 3.5% Discounting benefits: 3.5%	Mepolizumab add-on to standard therapy Standard therapy [Omalizumab add-on to standard therapy in an overlap population§§§]	Adults with severe, refractory eosinophilic asthma on high-dose ICS and additional maintenance treatment(s)	**Total costs** CIC in manufacturer's submission	**QALY** CIC in manufacturer's submission	**ICER [cost/QALY]** ***Manufacturer submission*** Mepolizumab vs standard therapy • Manufacturer proposed population¶¶¶, £19,526 • As above, but excluding maintenance OCS users with <4 exacerbations, £15,394

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
UK	Health states • Day-to-day symptoms; people on treatment • Day-to-day symptoms; people 'responding' and continuing add-on biologic treatment • Day-to-day symptoms; people not 'responding' to add-on biologic treatment, standard therapy alone • Asthma-related mortality • All-cause mortality					• ITT, £31,659 ***ERG reanalysis*** Mepolizumab vs standard therapy • Manufacturer proposed population¶¶¶, £35,440 • As above, but excluding maintenance OCS users with <4 exacerbations, £33,520 • ITT, £72,596 **Mepolizumab vs omalizumab and vs standard therapy in the overlap ITT population**§§§ • Mepolizumab dominated • Standard therapy: £105,455
NICE TA479 2017 (NICE 2017) UK	Markov model Time horizon, Lifetime	Reslizumab add-on to standard therapy Standard therapy	Adult patients at GINA Steps 4 and 5 who had experience ≥3	**Total costs [£, 2015]** ***Manufacturer submission*** • Reslizumab, CIC	**QALY** ***Manufacturer submission*** • Reslizumab, 15.08	**ICER** ***Manufacturer submission*** **Cost/QALY**

Citation, country	Summary of model	Intervention/ comparator	Patient population	Base case costs [currency, year]	Base case health outcomes	Base case ICER
	Perspective, Payer Cycle length, 4 weeks Discounting costs: 3.5% Discounting benefits: 3.5% Health states • Controlled asthma • Uncontrolled asthma • Moderate exacerbation • Severe exacerbation • Asthma-related mortality • All-cause mortality		exacerbations in the preceding year	• Standard therapy, £83,417 ***Revised base case*** • Reslizumab, CIC (additional costs of £65,673) • Standard therapy, £61,713	• Standard therapy, 11.99 ***Revised base case*** • Reslizumab, 15.84 • Standard therapy, 13.64	Reslizumab vs standard therapy, £24,907 Omalizumab vs standard therapy, £33,254 Reslizumab vs omalizumab, £16,643 **Cost/LYG** Reslizumab vs standard therapy, £22,367 ***Revised base case* Cost/QALY** Reslizumab vs standard therapy, £29,870 ***ERG response* Cost/QALY** Reslizumab vs standard therapy, £57,356

B.3.2 Economic analysis

As no economic analyses of the cost effectiveness of benralizumab as add-on therapy to high-dose ICS/LABA were identified from the SLR, a *de novo* economic model has been developed.

B.3.2.1 Patient population

The economic evaluation addresses the Decision Problem (Section B.1.1) and seeks to explore the cost-effectiveness of add-on benralizumab compared with SoC alone (or versus add-on mepolizumab or reslizumab in their respective NICE recommended populations) in adults with severe refractory eosinophilic asthma. These people are considered to be receiving maximal inhaled therapy (high dose ICS and additional maintenance treatment[s]). As a cohort, it should be noted that a proportion of patients will be on maintenance OCS (mOCS) (see Table 39).

Add-on benralizumab showed enhanced clinical benefit in sub-populations of the anticipated licensed indication (see Section B.2.7). This was demonstrated in patient populations with a persistent blood eosinophil count of ≥300 cells/μL and ≥3 exacerbations in the previous year. Benralizumab also demonstrated the reduction of mOCS dose which is desirable because of the adverse events associated with both short and long-term use. In order to maximise the clinical benefit of benralizumab, to align with clinical expert opinion on the positioning of anti-IL-5 medicines and in the context of the current guidance for other biologics for severe asthma we seek a recommendation for benralizumab from the Committee as an option for:

Patients with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per μl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with mOCS over the previous 6 months.

This will be referred to from now on as the “Base Case Population”.

B.3.2.2 Model structure

The model structure is detailed below in Figure 28. Patients enter the model and are classified according to whether they are treated with mOCS or not ("Background Therapy" in the figure). These patients then enter the pre-response assessment phase ("Treatment Phase" in the figure) of the model for the first 52 weeks of treatment, during which time patients transition through states as per the below definitions at the pre-response assessment probabilities ("Health States" in the figure). Then at 52 weeks patients are assessed for their treatment response (detailed below) and are either defined as having a treatment response or not ("Treatment Phase" in the figure), after which all patients transition through states ("Health States" in the figure) based on post response transition probabilities in 2 weekly cycles due to the frequency of ACQ capture in the trials Table 37.

Health State Definitions

The definition of health states is summarised below, and their actual assessment schedule by trial is shown in Table 37:

- Controlled Asthma: ACQ-6 score <1.5 (as with precedent from the reslizumab NICE STA)
- Uncontrolled Asthma: ACQ-6 score ≥1.5
- Exacerbations:
  - **OCS burst only**: Use of systemic corticosteroids (or a temporary increase in a stable mOCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids, with no hospitalisation.
  - **Emergency Visit**: An urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as above) with no hospitalisation.
  - **Hospital admission:** An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

Table 37: Clinical assessments to define health states, by study

Measure	Study		
	SIROCCO (48 weeks treatment period)	**CALIMA (56 weeks treatment period)**	**ZONDA (28 weeks treatment period)**
Eosinophil counts at baseline	Measured		
mOCS use at baseline	With and without mOCS use at baseline		All using mOCS at baseline per inclusion criteria
FEV_1 (Pre)	Weeks 0, 4 and 8, then every 8 weeks		Every 4 weeks
ACQ-6 score	Measured every 2 weeks/reflects previous week		
Exacerbations	Start date of exacerbation		

ACQ-6=Asthma Control Questionnaire 6; FEV1=forced expiratory volume in 1 second; OCS=oral corticosteroids.

All patients are assumed to start in the Uncontrolled Asthma state.

Assessment of response to treatment

Within the economic model it is assumed that, as with clinical practice and current NICE recommendations for biologic therapies, there will be a clinical assessment of response to treatment. This is assumed to occur at 52 weeks, in accordance with clinical expert advice and in keeping with current NICE recommendations for mepolizumab and reslizumab, and is defined as below:

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

It is assumed that after this assessment of response, patients who meet the response criteria will continue treatment with benralizumab and benefit from improved efficacy, while patients who do not meet the response criteria will discontinue benralizumab and will revert to standard of care costs and efficacy.

Figure 28: Model structure

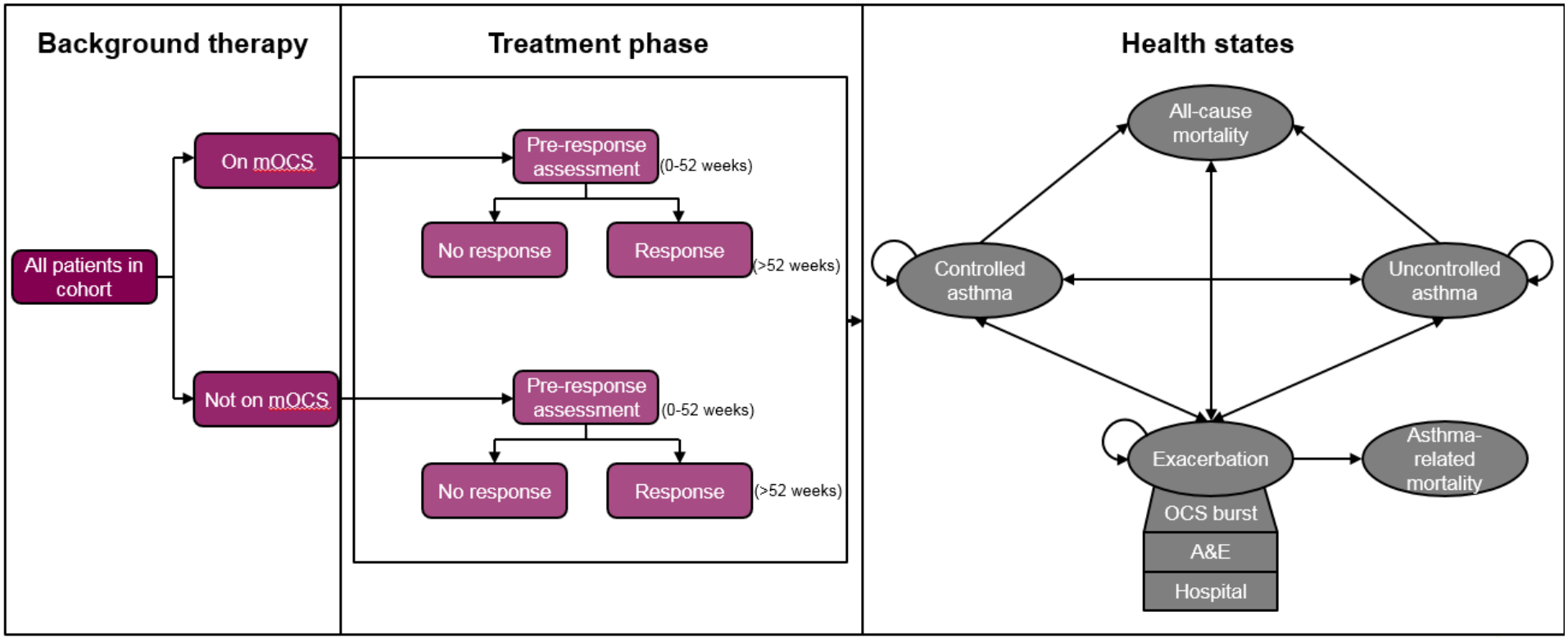


Table 38: Features of the economic analysis base case, as compared with previous appraisals

	Previous appraisals		Current appraisal	
Factor	**TA431 - Mepolizumab for treating severe refractory eosinophilic asthma (NICE 2017)**	**TA479 - Reslizumab for treating severe eosinophilic asthma (NICE 2017)**	**Chosen values**	**Justification**
Time horizon	Lifetime	60 years (assumed to be equivalent to lifetime)	Lifetime	Long enough to reflect all important differences in costs or outcomes between technologies. Reflective of clinical practice.
Model Structure	3 state model based on exacerbations and the assumption of increased QoL outside of exacerbations	5 State model including Controlled and Uncontrolled Asthma, Exacerbations are either Moderate or Severe	4 state model including Controlled and Uncontrolled Asthma and Exacerbations. As per model used in Reslizumab appraisal, removing the Moderate Exacerbation state	Model structure accepted by previous NICE STA of reslizumab, follows clinical expert opinion that the difference between a moderate exacerbation and uncontrolled asthma would be imperceptible
Assessment of Treatment Response	A 50% reduction in the number of exacerbations or a reduction in continual use of mOCS after 52 weeks of treatment	A reduction in the number of exacerbations or a reduction in continual use of mOCS after 52 weeks of treatment	A reduction in the number of exacerbations or a reduction in continual use of mOCS after 52 weeks of treatment	As per precedent set in the reslizumab NICE STA and aligns to clinical expert preference on the definition and time point
Treatment waning effect	Not included	Not included	Not included	No evidence of treatment effect waning. Consistent with other appraisals in the disease area
Source of utilities	EQ-5D from DREAM trial	Mapped utility from AQLQ from pooled trials	EQ-5D from pooled SIROCCO/CALIMA and mapped AQLQ from ZONDA	Consistent with Reference case

Source of costs	PSSRU and NHS reference costs	PSSRU and NHS reference costs	PSSRU and NHS reference costs	Consistent with Reference case
Cycle length	4 weeks	4 weeks	2 weeks	Consistent with frequency of measurement in the trials
Measurement of Health Effects	QALYs	QALYs	QALYs	Consistent with Reference case
Discount Rate assumed for utilities and costs	3.5%	3.5%	3.5%	Consistent with Reference case
Perspective	NHS	NHS	NHS	Consistent with Reference case

B.3.2.3 Intervention technology and comparators

Intervention: Add-on Benralizumab

Add-on benralizumab is a 30mg 8-weekly subcutaneous (SC) injection with an initiation phase of 4-weekly dosing for the first 3 doses, for severe refractory eosinophilic asthma adult patients (≥18 years), already on high dose ICS and additional maintenance treatments(s). We seek guidance for a sub-population of the marketing authorisation for patients who have a blood eosinophil count of ≥300 cells/μL at initiation of treatment; and ≥3 exacerbations in the previous year or are dependent on mOCS (see the Decision Problem in Section B.1.1).

Comparator 1: SoC alone

Clinical inputs for the SoC alone arm of the model is derived from the SoC arm of the pooled SIROCCO/CALIMA trials for patients not receiving mOCS and from ZONDA for those patients who are receiving mOCS. Patients are on high dose ICS and an additional maintenance treatment(s) (such as LABA, leukotriene receptor antagonist or theophylline). Clinician feedback from an advisory board considered the SoC arms of the pooled SIROCCO/CALIMA and ZONDA trials to fairly reflect SoC in clinical practice in England and Wales and those treatments outlined in the BTS/SIGN guidelines. These patients have limited alternative treatment options beyond mOCS.

Comparator 2: Add-on mepolizumab

Mepolizumab (Nucala) is a humanised monoclonal antibody indicated in adults as add-on therapy in patients with severe refractory eosinophilic asthma. The recommended dose of mepolizumab is 100 mg, it is available as a lyophilised white powder and administered subcutaneously every 4 weeks. NICE recommends mepolizumab in a sub-population of the licensed indication (NICE 2017):

"Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- *the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and*
- *the person has agreed to and followed the optimised standard treatment plan and*
  - *has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or*
  - *has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months"*

This will be the population in which the comparison of benralizumab vs mepolizumab will be made and will henceforth be referred to as the "mepolizumab NICE recommended population".

No person would receive both biologic treatments concurrently.

Comparator 3: Add-on reslizumab

Reslizumab (Cinqaero) is a humanised monoclonal antibody indicated in adults as add-on therapy in patients with severe refractory eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. The recommended dose of reslizumab varies from patient to patient and is determined based on a patient's body weight, it is available as an intravenous infusion and administered every 4 weeks. NICE recommends reslizumab in a sub-population of the licensed indication (NICE 2017):

"Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:

- *the blood eosinophil count has been recorded as 400 cells per microlitre or more*
- *the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months"*

This will be the population in which the comparison of benralizumab vs reslizumab will be made and will henceforth be referred to as the "reslizumab NICE recommended population"

No person would receive both biologic treatments concurrently.

B.3.3 Clinical parameters and variables

Standard of Care

Clinical data (exacerbation rates, quality of life and transition probabilities based on ACQ score) were derived from three benralizumab trials, a pooled analysis of CALIMA and SIROCCO for patients not on mOCS (published and unpublished data) and ZONDA for patients who are on mOCS. Inputs were extracted from the afore mentioned trials (add-on benralizumab versus SoC alone)

An advisory board was conducted in July 2017 with the primary aim to assess the benralizumab clinical trial data and its relevance to the UK clinical practice and secondly to test the structure and clinical data and assumptions that underpin the economic model.

Mepolizumab

As stated previously the NICE recommendation for mepolizumab is in patients in whom the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and

- the person has agreed to and followed the optimised standard treatment plan and
- has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
    - has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months
    - Given this recommendation it follows that the appropriate comparison of benralizumab and mepolizumab would occur within this recommended population.

In the absence of a head to head trial between benralizumab and mepolizumab an indirect comparison was assessed for feasibility, however, due to there being no published data from mepolizumab in the mepolizumab NICE recommended population the only possible indirect comparison is between the full trial populations.

During the feasibility assessment, it was observed that there were key differences within the two trial populations in terms of baseline characteristics (Section B.2.9), and these were felt to be potential treatment effect modifiers.

Based on these observations it was determined that the most robust approach to indirect comparison would be to undertake a Matched Adjusted Indirect Comparison (MAIC) as per NICE DSU guidance (Phillippo 2016) (benralizumab versus mepolizumab; see section B.2.9: results).

Reslizumab

As stated previously the NICE recommendation for reslizumab is in patients in whom

- the blood eosinophil count has been recorded as 400 cells per microlitre or more
- the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months

Given this recommendation it follows that the appropriate comparison of benralizumab and reslizumab would occur within this recommended population.

In the absence of a head to head trial between benralizumab and reslizumab an indirect comparison was assessed for feasibility, however, due to there being very limited published data from reslizumab in their recommended population the best possible indirect comparison is between the full trial populations.

During the feasibility assessment, it was observed that there were key differences within the two trial populations in terms of baseline characteristics (Section B.2.9), and these were felt to be potential treatment effect modifiers.

Based on these observations it was determined that the most robust approach to indirect comparison would be to undertake a Matched Adjusted Indirect Comparison (MAIC) as per NICE DSU guidance.

However, due to such significant differences between the trials, the population in which a MAIC could be conducted was significantly reduced to 20 patients and was therefore determined not to be feasible. Clinical data inputs, therefore, in this comparison are assumed to be equivalent between benralizumab and reslizumab.

Mortality

Asthma-related mortality was extracted from published peer reviewed sources (Watson et al. 2007, Roberts et al. 2013, NRAD 2014) and all-cause mortality was applied from life tables.

B.3.3.1 Patient characteristics

Table 39 shows the baseline characteristics which affect outcomes implemented in the model which were derived from pooled SIROCCO/CALIMA as this represents the largest sample size and does not differ significantly from the baseline characteristics observed in the ZONDA trial. At baseline, the mean age was 50.2 years and 64.5% of patients were female. In order to calculate the percentage of patients in each population who would be dependent on mOCS at baseline in UK clinical practice, an analysis of the Kerkhof 2017 paper, a UK observational research study, was undertaken. For a full description of the baseline characteristics refer to Table 22.

Table 39 Patient characteristics at baseline, inputted into model, Base Case Population

Characteristic	Value inputted	Source
Age	50.2	SIROCCO/CALIMA
% female	64.5%	SIROCCO/CALIMA
% patients on mOCS	54.1%	DOF

Table 40: Patient characteristics at baseline, inputted into model, Mepolizumab NICE recommended population

Characteristic	Value inputted	Source
Age	49.8	SIROCCO/CALIMA
% female	66.1%	SIROCCO/CALIMA
% patients on mOCS	78.6%	DOF

Table 41: Patient characteristics at baseline, inputted into model, Reslizumab NICE recommended population

Characteristic	Value inputted	Source
Age	50.2	SIROCCO/CALIMA
% female	63.3%	SIROCCO/CALIMA
% patients on mOCS	0%	Reslizumab for treating severe eosinophilic asthma (TA479)

B.3.3.2 Transition probabilities

Controlled and Uncontrolled Asthma

Transition probabilities were derived from the 2-weekly ACQ-6 follow up of patients, based on the pooled SIROCCO/CALIMA and ZONDA trials. Patients were initially allocated to either Controlled or Uncontrolled asthma states within each post-randomisation 2-week cycle, i.e. 0–2 weeks, 2–4 weeks etc. The Controlled and Uncontrolled health states were determined using the ACQ-6 score at the end of each 2-week cycle as described in Section B.3.2.2.

Exacerbations

A recent publication (Golam 2017) showed that the utility decrement in patients in the SIROCCO and CALIMA trials experiencing an exacerbation lasted for between 7 and 10 weeks.

This post-hoc analysis used pooled data from two pivotal studies of benralizumab, SIROCCO and CALIMA. The SIROCCO trial evaluated benralizumab anti-eosinophil treatment regimens of 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W, first three doses every 4 weeks) vs. placebo in combination with high-dosage inhaled corticosteroids (ICS)/long-acting β2-agonists (LABA) for 48 weeks in patients with severe asthma.

The analysis used the following endpoints from SIROCCO and CALIMA:

- The EuroQoL 5 dimensions, 5 levels (EQ-5D-5L), a generic health status instrument
- Asthma exacerbation events treated by:
    - OCS burst
    - ED visits
    - Hospitalisations

Different health states from the weekly EQ-5D-5L responses were converted to utility values (scalars that combine all five dimensions of the EQ-5D-5L) by using values/preferences for health states that were derived from a sample of the United Kingdom (UK) general population.

All patients with an exacerbation were selected from the pooled SIROCCO and CALIMA data

To calculate utility during an exacerbation, several steps were taken:

- The exacerbation starting date as documented in the study protocol/clinical electronic case report form (eCRF) was defined as Day 0

- EQ-5D-5L utility values collected within ±3 days of Day 0 were used to calculate the average utility, which was considered to be the Week 0 average
- To measure mean utility values before and after the start of exacerbations, we calculated weekly averages (e.g., Week −2, −1, +1, +2, etc.; Figure 1)
- Mean utilities using only the EQ-5D-5L values during the protocol-defined exacerbation periods were calculated as well.
    - The benralizumab study protocols define the start of an exacerbation as the earliest of the following: 1) the start date of OCS or a temporary increase in a stable mOCS background dosage, 2) the date of an ED visit, or 3) the date of hospital admission
    - The end date is defined as the latest (i.e., most recent) of the following: 1) the last day of systemic corticosteroids or a temporary increase in a stable mOCS background dosage, 2) the date of ED discharge, or 3) the date of hospital discharge

Durations across the three exacerbation event types were based on a visual inspection of mean utilities per week. Durations encompassed the week during which the mean utility starts to decline through the week during which the mean utility returns to a stable level.

Based on this analysis we have therefore reflected this in the model by allocating the exacerbation health state to the 4 cycles that best fit within ±4 weeks of the exacerbation start date, i.e. 8 weeks in total. To implement this, the exacerbation start date was adjusted to match the closest cycle start date. The 2 cycles before and 2 cycles after that start date were then defined as ‘exacerbation cycles’. Additionally, only the transition into and out of the exacerbation health state was used, effectively collapsing the 4 cycles per exacerbation into 1 cycle.

Further analysis of utility data using the above method was conducted on the utility score during an exacerbation dependent on which state a patient had been in prior to suffering an exacerbation. It was observed that the utility decrement for exacerbations differed based on whether that patient was Controlled or Uncontrolled prior to having the exacerbation, therefore this is reflected in the model (denoted in the tables below as “Exacerbation (Controlled)” and “Exacerbation (Uncontrolled)”. This approach is used as we believe that applying a single utility value for all exacerbations would overstate the utility decrement for patients having an exacerbation while previously being controlled and understate the utility decrement for patients having an exacerbation while previously being uncontrolled. This follows precedent from a previous appraisal in the respiratory area for roflumilast (TA 461) where differential utility values were applied to patients experiencing an exacerbation dependent on their COPD severity.

Given that exacerbations are assessed over an 8-week period, while asthma control and transition to exacerbations are assessed on a 2-weekly basis, the transition probability matrix based on 2-weekly model cycle interpretation reflects a 4 times higher than actual probability of entering an exacerbation state that lasts 4 times shorter than the actual length of time in that state. This means that model calculations track patients to enter 2 weekly exacerbations states 4 times repeatedly, resulting an exacerbation duration of 8 weeks in line with the trial data. This is discussed further in Section B.3.4.

The two-week transition probabilities used in the base case model for transition between health states for benralizumab and the relevant comparators are outlined below.

B.3.3.2.1 Standard of Care comparison – Base Case Population

Non mOCS

The base case transition probabilities for patients not receiving mOCS were computed using patient level data from two pooled benralizumab clinical trials (SIROCCO/CALIMA). The total pooled population from these trials included 986 patients, of which 496 were treated with SoC and 490 with benralizumab. Analysis was limited to patients in the Base Case Population, i.e. those who were ≥18 years of age, using 800ug ICS fluticasone equivalent per day, having an eosinophil count of greater than or equal to 300 cells per µL and having experienced 3 exacerbations or more in the preceding year, giving a population of 136 in the SoC treatment arm and 123 in the benralizumab arm.

Table 42: Transition probabilities – SoC (non mOCS), Base Case Population, All Weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Two different transition matrices were computed for the benralizumab treatment arm, according to the assumptions of the model:

- Transition probabilities from 0–52 weeks for the base case population benralizumab-treated population using pooled SIROCCO/CALIMA
- Transition probabilities after 52 weeks for responders, in the base case population, to benralizumab treatment using pooled SIROCCO/CALIMA

Assessment of response to treatment

As described in Section B.2.3, assessment of response was made at 52 weeks based on:

- a clinically meaningful reduction in the number of exacerbations needing systemic corticosteroids

The distribution of the benralizumab-treated population, in terms of treatment response is presented in Table 43. The base case analysis assumes that non-responders do not continue treatment beyond 52 weeks and revert to SoC costs and effects.

Table 43: Percentage of patients responding to benralizumab (non mOCS)

	Responders	**Non-Responders**
Benralizumab (Non mOCS)	[redacted]	[redacted]

Pre-Response Assessment (0-52 weeks)

The pre-assessment transition probabilities were computed using data from the base case benralizumab treated population before assessment of response at 52 weeks. The results are presented in Table 44 and Table 45.

Table 44: Transition probabilities – Benralizumab (non mOCS), Base Case Population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Post-Response Assessment (>52 weeks)

In the benralizumab treatment arm, patients who do not meet the criteria for response are assumed to discontinue treatment and transfer to the SoC arm. As data beyond 52 weeks of treatment with benralizumab were not available, all transition probabilities, including exacerbations beyond 52 weeks were based on data reported (0-52 weeks) in responders according to the definition described above.

Table 45: Transition probabilities – Benralizumab responder (non mOCS), Base Case Population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

mOCS

The base case transition probabilities for patients receiving mOCS were computed using patient level data from the OCS sparing benralizumab clinical trial (ZONDA). The total population from this trial included 148 patients, of which 75 were treated with SoC and 73 with benralizumab. Analysis was limited to patients who were ≥18 years of age and having an eosinophil count of greater than or equal to 300 cells per µL, giving a population of 64 in the SoC treatment arm and 61 in the benralizumab arm.

Table 46: Transition probabilities – SoC (mOCS), Base Case Population, All Weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Two different transition matrices were computed for the benralizumab treatment arm, according to the assumptions of the model:

- Transition probabilities from 0–52 weeks for the base case population benralizumab-treated population using ZONDA
- Transition probabilities after 52 weeks for responders, in the base case population, to benralizumab treatment using ZONDA

Assessment of response to treatment

As described in Section B.3.2, assessment of response was made at 52 weeks based on:

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

The distribution of the benralizumab-treated population, in terms of treatment response is presented in Table 43. The base case analysis assumes that non-responders do not continue treatment beyond 52 weeks and revert to SoC costs and effects.

Table 47: Percentage of patients responding to benralizumab (mOCS)

	Responders	**Non-Responders**
Benralizumab (mOCS)	[redacted]	[redacted]

Pre-Responder Assessment (0-52 weeks)

The pre-assessment transition probabilities were computed using data from the base case benralizumab treated population before assessment of response at 52 weeks. The results are presented in Table 48 and Table 49.

Table 48 Transition probabilities – Benralizumab (mOCS), Base Case Population, 0-52 weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Post-Response Assessment (>52 weeks)

In the benralizumab treatment arm, patients who do not meet the criteria for response are assumed to discontinue treatment and transfer to the SoC arm. As data beyond 52 weeks of treatment with benralizumab were not available, transition probabilities beyond 52 weeks were based on data (0-52 weeks) reported in responders according to the definition described above.

Table 49: Transition probabilities – Benralizumab responder (mOCS), Base Case Population, >52 weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

B.3.3.2.2 Mepolizumab Comparison – Mepolizumab NICE recommended population

As described in Section B.3.3, a MAIC was conducted to estimate the relative exacerbation rates of add-on benralizumab compared with add-on mepolizumab. Given the limitations of the available evidence for mepolizumab, the comparison versus mepolizumab was performed in the full trial populations for benralizumab and mepolizumab (see Section B.2.9). The results showed that benralizumab [redacted] mepolizumab for the relevant endpoints (exacerbations, FEV1, exacerbations leading to hospitalisation and relative OCS sparing. We consider it reasonable to assume that the relative efficacy between the drugs will be the same in the all-comers trial population as in the more severe sub-group; and we have not identified any reasons/clinical rationale against this assumption. Further, since both drugs show greater efficacy in more severe patients, i.e., as EOS increases and exacerbation frequency increases, we would expect the difference in effect seen in the ITT populations to remain in place in the more severe sub-group. This approach is in line with the assumptions made in both of the previous appraisals in severe asthma where mepolizumab and reslizumab were compared to omalizumab (TA431 and 479). The corresponding rate ratios versus placebo for clinically significant exacerbations were estimated at [redacted] for add-on benralizumab versus add on mepolizumab in the non-mOCS population (Table 50) and [redacted] for the mOCS population (Table 51). To derive the exacerbation rate for mepolizumab, 1/the MAIC RR is applied to the exacerbation rate observed in the benralizumab arm of pooled SIROCCO/CALIMA and ZONDA data, using data for the mepolizumab NICE recommended population (Section B.3.2).

Table 50: MAIC results for SIROCCO/CALIMA versus MENSA/DREAM

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched): RR (95% CI)	
SIROCCO/CALIMA vs. MENSA/DREAM	Annualised rate of clinically significant exacerbations	[redacted]	[redacted]
	FEV_1	[redacted]	[redacted]
	Annualised exacerbation rate leading to ER/hospitalisation	[redacted]	[redacted]

* High-dose ICS populations (≥ 880 µg FP daily SIROCCO/CALIMA vs MENSA/DREAM) adjusted for trial differences.
MAIC includes benralizumab 30 mg Q8W SC data vs mepolizumab 100mg Q4W SC & 75mg Q4W IV (bioequivalent dose) data

Table 51: MAIC results for ZONDA versus SIRIUS

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

* High-dose ICS populations (>500 µg FP daily ZONDA vs SIRIUS) adjusted for trial differences.
MAIC includes benralizumab 30 mg Q8W SC data vs mepolizumab 100mg Q4W SC & 75mg Q4W IV (bioequivalent dose) data

NICE guidance for mepolizumab also recommends a stopping criterion based on an assessment at 52 weeks (NICE 2017). As evidence for the effectiveness of mepolizumab in patients who meet the treatment continuation criteria is unpublished and unavailable, exacerbation rates of those who continue or discontinue treatment could not be indirectly compared. For mepolizumab, these values have been assumed to also follow the relative rates found in the MAIC, while all patients who discontinue treatment are assumed to follow the exacerbation rates and transition probabilities of the SoC arm in the benralizumab trial. Evidence from the mepolizumab NICE STA (NICE 2017) is considered to be the most relevant source from which to determine the percentage of patients responding to treatment with mepolizumab because it is the only publicly available source in which this treatment response rate has been evaluated in the correct population. As the data regarding the percentage of patients responding to mepolizumab is not specific as to whether it applies to the non mOCS or the mOCS population and it is referenced to the MENSA/DREAM trials it is assumed that this percentage relates to the non mOCS population and an assumption is made that the percentage of responders in the mOCS population is equal that of benralizumab. A summary of the percentage of responders by treatment is shown in Table 52.

Table 52: Percentage of patients responding to biologic therapy (benralizumab and mepolizumab)

	Population	Responders	Non-Responders
Benralizumab	Non OCS	[redacted]	[redacted]
	mOCS	[redacted]	[redacted]
Mepolizumab	Non OCS	[redacted]	[redacted]
	mOCS	[redacted]	[redacted]

* As no information is available for the percentage of patients responding to mepolizumab in the mOCS population, this is assumed to be equal to that of benralizumab

Non mOCS

Transition probabilities for benralizumab and mepolizumab in the mepolizumab NICE recommended population in patients not treated with mOCS for the pre and post response assessment periods are detailed below.

Pre-Response Assessment (0-52 weeks)

Table 53: Transition probabilities – Benralizumab (non mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 54: Transition probabilities – Mepolizumab (non mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Post Response Assessment (52 weeks)

Table 55: Transition probabilities – Benralizumab responder (non mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 56: Transition probabilities – Mepolizumab responder (non mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 57: Transition probabilities – SoC (non mOCS), Mepolizumab NICE recommended population, All Weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

mOCS

Transition probabilities for benralizumab and mepolizumab in the mepolizumab NICE recommended population in patients receiving mOCS for the pre and post response assessment periods are detailed below.

Pre-Response Assessment (0-52 weeks)

Table 58: Transition probabilities – Benralizumab (mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 59: Transition probabilities – Mepolizumab (mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Post-Response Assessment (>52 weeks)

Table 60: Transition probabilities – Benralizumab responder (mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]

	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 61: Transition probabilities – Mepolizumab responder (mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 62: Transition probabilities – SoC (mOCS), Mepolizumab NICE recommended population, All weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

B.3.3.2.3 Reslizumab Comparison – Reslizumab reimbursed population

As mentioned in Section B.3.3, due to significant trial differences, we were unable to robustly conduct a MAIC to compare add on benralizumab with add on reslizumab. In order to facilitate a comparison between these two products, therefore, we have made the assumption that all clinical values, and therefore transition probabilities are equivalent between the two products.

Reslizumab also has stopping criteria based on an assessment at 52 weeks. As evidence for the effectiveness of reslizumab in patients who meet the treatment continuation criteria is unpublished, exacerbation rates of those who continue or discontinue treatment could not be indirectly compared. For add on reslizumab, these values have been assumed to also be equivalent to those of add-on benralizumab, while all patients who discontinue treatment are assumed to follow the exacerbation rates and transition probabilities of the SoC arm in the benralizumab trial. Given the response assessments for reslizumab and benralizumab are the same and that the clinical inputs for the two products are also the same, it is reasonable therefore to assume that the same percentage of patients will respond to each medicine. A summary of the percentage of responders by treatment is shown in Table 63.

Table 63: Percentage of patients responding to biologic therapy (benralizumab and reslizumab), reslizumab NICE recommended population

	Population	Responders	Non-Responders
benralizumab	Non mOCS	[redacted]	[redacted]
reslizumab	Non mOCS	[redacted]	[redacted]

Due to the absence of an OCS sparing study for reslizumab and the NICE recommendation not being inclusive of patients using mOCS, the comparison between benralizumab and reslizumab is only conducted in the non mOCS patient population.

Non mOCS

Transition probabilities for benralizumab and reslizumab in the reslizumab NICE recommended population for patients no treated with mOCS, pre and post assessment periods are detailed below.

Pre-Response Assessment (0-52 weeks)

Table 64: Transition probabilities – Benralizumab (non mOCS), reslizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 65: Transition probabilities – Reslizumab (non mOCS), reslizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Post Assessment (>52 weeks)

Table 66: Transition probabilities – Benralizumab responder (non mOCS), reslizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 67: Transition probabilities – Reslizumab responder (non mOCS), reslizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 68: Transition probabilities – SoC (non mOCS), Reslizumab NICE recommended population, All weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

B.3.3.3 Distribution of exacerbations

An analysis of exacerbations in the trial data was performed, and it was observed that benralizumab not only reduces the frequency of exacerbations but also the severity of those exacerbations in terms of a lower frequency of hospitalisations. Data from the SIROCCO/CALIMA (pooled) and ZONDA trials were therefore used to reflect this in the model and to derive the percentage (%) of each type of exacerbation by taking the number of exacerbations in each treatment group and dividing by the total number of exacerbations (Table 69).

Table 69: Exacerbation distribution extracted from pooled clinical trial data, Base Case population

Parameter	N	%	Source
Controlled			
Benralizumab - mOCS			
OCS treated exacerbations	3	100	ZONDA
Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Benralizumab - Non mOCS			
OCS treated exacerbations	16	100	SIROCCO/CALIMA
Exacerbations treated in the ER	0	0	SIROCCO/CALIMA
Exacerbations treated in hospital	0	0	SIROCCO/CALIMA
Uncontrolled			
Benralizumab - mOCS			
OCS treated exacerbations	13	100	ZONDA

Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Benralizumab - Non mOCS			
OCS treated exacerbations	22	81.48	SIROCCO/CALIMA
Exacerbations treated in the ER	0	0	SIROCCO/CALIMA
Exacerbations treated in hospital	5	18.52	SIROCCO/CALIMA
Controlled			
Standard Care - mOCS			
OCS treated exacerbations	21	100	ZONDA
Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Standard Care - Non mOCS			
OCS treated exacerbations	25	89.29	SIROCCO/CALIMA
Exacerbations treated in the ER	1	3.57	SIROCCO/CALIMA
Exacerbations treated in hospital	2	7.14	SIROCCO/CALIMA
Uncontrolled			
Standard Care - mOCS			
OCS treated exacerbations	31	68.89	ZONDA
Exacerbations treated in the ER	5	11.11	ZONDA
Exacerbations treated in hospital	9	20	ZONDA
Standard Care - Non mOCS			
OCS treated exacerbations	99	85.34	SIROCCO/CALIMA
Exacerbations treated in the ER	9	7.75	SIROCCO/CALIMA
Exacerbations treated in hospital	8	6.91	SIROCCO/CALIMA

'mOCS use' and 'non mOCS' use refer to use of mOCS as part of baseline therapy.

For the comparisons of benralizumab versus other biologics, it is assumed that the split of exacerbations is the same for all comparators, by applying the split for benralizumab patients to mepolizumab and reslizumab patients.

B.3.3.3.1 Consequences of mOCS

In order to quantify the impact of Oral Corticosteroids (OCS) exposure, AstraZeneca commissioned a matched historical cohort study using the Optimum Patient Care Research Database (OPCRD), and the Clinical Practice Research Datalink (CPRD) database (AstraZeneca data on file 2017). The study consisted of a minimum 1-year baseline period and a minimum 2 years' outcome period, on either side of an index date. The index date was the date of the first recorded prescription for a parenteral or oral corticosteroid for patients in the mOCS arm, while that for the non mOCS arm was the nearest primary care visit to the matched-case index date.

Complete and partial mOCS sparing was assessed in the ZONDA trial and results for both benralizumab and placebo arms were reported for different categories of daily mOCS exposure (i.e., 0mg, >0 to <0.5mg, 0.5mg to <2.5mg, 2.5mg to <5mg, 5mg to <7.5mg, 7.5mg to <15mg, ≥15mg) at baseline and at 28 weeks.

Complete and partial mOCS sparing is calculated for the benralizumab vs mepolizumab comparison via the MAIC.

Table 70: Percentage of patients by mean daily mOCS dose

Daily dose of mOCS (mg)	Benralizumab		Placebo	
	Baseline	At 28 weeks	Baseline	At 28 weeks
0 (no mOCS)	[redacted]	[redacted]	[redacted]	[redacted]
>0 - <0.5	[redacted]	[redacted]	[redacted]	[redacted]
0.5 - <2.5	[redacted]	[redacted]	[redacted]	[redacted]
2.5 - <5	[redacted]	[redacted]	[redacted]	[redacted]
6 - <7.5	[redacted]	[redacted]	[redacted]	[redacted]
7.5 - <15	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]

Throughout the model, patients receiving mOCS treatment are at risk of developing the comorbidities which are associated to mOCS use. During the first 28 weeks (the length of the ZONDA trial) period patients are assumed to receive mOCS according to the percentages seen at baseline in the ZONDA trial, after the initial 28-week period patients are assumed to receive mOCS according to the percentages seen at the end of the ZONDA trial for the remainder of the model duration (Table 70).

To adjust for the presence of chronic conditions in the cohort of mOCS users, period prevalence and incidence data of different comorbidities for the same categories of daily mOCS dose were sourced from data From the AstraZeneca RWE study detailed above (AstraZeneca data on file 2017). The risk of the 10 comorbidities included in the analysis and the risk/dose relationship over a 15 year period is shown below (Table 71)

Table 71: Period prevalence or incidence of comorbidities among asthma patients (AstraZeneca data on file 2017)

Daily dose of mOCS (mg)	Type 2 diabetes mellitus	Osteo-porosis	Glaucoma	Cataract	Myocardial infarction	Heart failure	Cerebro-vascular accident	Renal impairment	Peptic ulcer	Pneu-monia
>0 - <0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5 - <2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 - <5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 - <7.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.5 - <15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.3.4 Discontinuations outside of the response assessment

Patients responding to add-on therapy are assumed to remain on the same add-on biologic for a lifetime duration, which is consistent with committee guidance for mepolizumab [ID798] and input from clinical advisers. However, there is likely to be a natural attrition rate in the number of patients (e.g. due to adverse events, personal or physician's preference) on treatment over the time horizon of the analysis. The economic model includes a set percentage of patients which discontinue treatment during each cycle. A percentage of both mOCS and non mOCS dependent patients move to 'Not on add-on treatment' each cycle according to the discontinuation of add-on therapy rate defined in the model inputs. Patients who discontinue treatment are assumed to continue receiving SoC and thus are assigned to SoC transition probabilities, utilities and costs. Discontinuation rates were sourced from clinical trial data and assumed to be the same for each add-on biologic, as per the precedent set in the recent NICE STA for mepolizumab (TA 431) and are outlined in Table 72.

Table 72: Percentage of patients discontinuing add-on therapy each year

Add-on therapy	Patients discontinuing therapy each year (%)	Probability of discontinuation per cycle	Source
Benralizumab	11.8%	0.0048	Pooled data from the phase III clinical trials for benralizumab. ITT population (Section B.2.4)
Mepolizumab	11.8%	0.0044	Assumed to be the same as benralizumab in keeping with the precedent in TA 431
Reslizumab	11.8%	0.0048	As discontinuation rate is not published in the reslizumab NICE guidance (NICE 2017), this is assumed to be the same as that for benralizumab.

B.3.3.5 Adherence to treatment

In the context of the economic model adherence describes the extent to which drug costs are included whilst 'on treatment' where 100% represents no missed days of therapy. For add-on benralizumab, mepolizumab and reslizumab treatment adherence is assumed to be 100% for those patients who continue on biologic therapy since treatment occurs at regular intervals in a clinical setting. This is consistent with the assumption made in the mepolizumab NICE STA TA431 and the reslizumab NICE STA TA479. People deemed at high risk of severe asthma attacks should be monitored more closely as part of their personal asthma action plans. This is a conservative assumption in the comparison of benralizumab vs SoC as it is likely to overstate drug costs

B.3.3.6 Mortality

Asthma-related mortality for all exacerbation states

Limited evidence on mortality in severe refractory eosinophilic asthma patients is captured by the benralizumab clinical trial programme, nonetheless asthma fatalities are still known to occur (refer to Section 1.3.1: burden of illness). In previous economic evaluations of mepolizumab and reslizumab, asthma-related mortality was identified as one of the key drivers of the cost-effectiveness vs. SoC alone. In the economic model, asthma related mortality is captured by a probability of dying related to experiencing an exacerbation. The source of mortality data is taken from Watson 2007, Roberts 2013 and the NRAD report (NRAD 2014).

A literature review of asthma-related mortality was conducted to identify UK studies reporting mortality rates as a result of severe asthma, or risk factors for asthma-related death. On inspection, only 2 studies were deemed informative, Watson 2007 and Roberts 2013.

The base case analysis uses data from Watson 2007, Roberts 2013 and the NRAD report. The study by Watson et al. was the only study to report mortality risk for acute severe asthma patients hospitalised for asthma. Data was analysed from the CHKS database, specifically admissions with ICD10 codes J45 (asthma, plus sub-codes J45.0, J45.1, J45.8 and J45.9) and J46 (acute severe asthma). Mortality during the admission spell (the period from a live admission to either discharge or death) was then recorded by admission code and stratified by age band (<12, 12–16, 17–44 and ≥45 years) and gender. One of the key limitations with this study is that in the absence of a death certificate the death could not be attributed to asthma with any certainty. However, it was deemed reasonable by Watson et al to assume that asthma was at least a contributory factor in the majority of deaths due to death occurring in the same admission spell, which lasted only a few days in the majority of patients. Time between admission and death was 4 days in acute severe asthma patients. Additionally, no secondary morbidity codes were reported for the patient in over 80% of cases.

The mortality risk reported by Watson et al. is a conditional probability; it represents the probability of death given a hospitalisation for asthma. In order to obtain the asthma-related mortality risk for hospitalised exacerbations in the economic analysis, the mortality risk following hospitalisation is multiplied by the risk of an exacerbation requiring a hospitalisation. Therefore, the age dependent risks are only applied following an exacerbation requiring hospitalisation.

Applying only an asthma related mortality risk to those experiencing an exacerbation requiring a hospitalisation was deemed a conservative approach, as it is known that patients die of asthma exacerbations outside of the hospital setting and benralizumab reduces exacerbations requiring hospitalisation and those requiring an A+E visit or an OCS burst. The NRAD report (identified through hand searching) is the first UK wide investigation into asthma deaths and the largest worldwide study of this kind to date. The aim was to understand circumstances surrounding asthma deaths and to identify avoidable factors and make recommendations for change and improvement in asthma care. The study was undertaken over a 3-year period (2011-2014). Extensive information about each death was sought from multiple sources including primary, secondary and tertiary care, as well as ambulance, paramedic and out of hours care providers. Death by location showed that 41% died at home, 23% on the way to hospital and 30% in hospital. Forty-five per cent (87/195) died from asthma without any medical assistance during the final episode; for 65 of these cases, there was no record of them seeking medical assistance, and for 22 cases (11%), there was a record of the patient trying to get help but dying before medical treatment could be provided.

NRAD is considered a valuable source of proxy mortality data for non-hospitalised mortality. It allows an estimation of probability of death for non-hospitalised exacerbation by combining location of death information with probabilities for death for hospitalised exacerbation (Watson 2007).

Asthma deaths from the exacerbation state were therefore calculated using data from (Watson et al. 2007, Roberts et al. 2013) and data from the National Review for Asthma Deaths (NRAD) (NRAD 2014).

The approach was optimised to reflect both the mortality attributable to asthma hospitalisation and the inherent variation in this risk across the most granular stratification of age categories available. The approach included the assumption that asthma-related mortality can only occur from the exacerbation state at specific asthma-related mortality rates. For exacerbations requiring a hospital admission, the model uses mortality data from Watson et al. (2007) combined with Roberts et al. (2013) and for exacerbations not requiring a hospital admission (i.e. OCS burst and ER visits) from Watson et al. (2007) combined with locations from the National Review for Asthma Deaths (NRAD) (Watson et al. 2007, Roberts et al. 2013, NRAD 2014). This approach is consistent with the preferred method used in the mepolizumab NICE STA (TA431) (NICE 2017).

Deriving probabilities of death given an exacerbation treated by an OCS burst or an A+E visit

Watson et al. reported mortality incidence, stratified by age, within an acute severe asthma population following a hospital admission, over a period of five years. However, this does not provide estimates for the probability of death for an exacerbation treated with either an OCS burst or an A+E visit. Therefore, for exacerbations not requiring a hospital admission (i.e. OCS burst and A+E visits) the data were combined with the results from the NRAD and the percentage of each type of exacerbation from the SIROCCO/CALIMA trials as outlined in Table 73, Table 74 and Table 75. The NRAD report only provides the percentage of deaths which occur from each type of exacerbation, however, the trial data shows that certain types of exacerbation are more frequent than others.

Table 73: Deaths during asthma-related hospital admission (Watson et al. 2007)

Age band (years)	Deaths during asthma admission	Total asthma admissions	Probability of death during asthma hospital admission (Watson et al. 2007)
17 – 44	36	9,407	0.00383
45 – 100	177	7,143	0.02478

Table 74: Location of asthma-related deaths (NRAD 2014)

Location of death (NRAD)	Number of people	Exacerbation type	Percentage of deaths during exacerbation (NRAD)
Home (private address)	80	OCS burst	46.67%
Nursing/residential home	5		
Holiday	4		
Other	2		
Hospital, pre-hospital arrest	45	ER visit	23.08%
Hospital, arrest in hospital	59	Hospital admission	30.26%

Table 75: Percentage of total exacerbations by type

Exacerbation Type	% of total exacerbations seen in pooled SIROCCO/CALIMA
OCS burst	86%
A+E	6.7%
Hospitalised	7.3%

Therefore, to calculate, for example the probability of death from an exacerbation treated with an OCS burst, the probability of death from a hospitalisation from Watson is adjusted by the percentage of deaths from a hospitalised exacerbation from NRAD and the percentage of exacerbations which were hospitalised in the trial data to give the probability of death from an exacerbation treated with an OCS burst adjusted by the % of deaths from an OCS treated exacerbation from NRAD and the % of exacerbations which were treated with an OCS burst from the trials – as per the formula below

$$\text{Probability of death (OCS burst)} \times \frac{\%\ \text{Exac (OCS burst)}}{\%\ \text{Deaths (OCS burst)}}$$
$$= \text{Probability of death (Hospital admission)} \times \frac{\%\ \text{Exac (Hosp)}}{\%\ \text{Deaths (Hosp)}}$$

Where % Exac (OCS) = Percentage of total exacerbations resulting in OCS burst (from SIROCCO/CALIMA), % Exac (Hosp) = Percentage of total exacerbations resulting in hospital admission (from SIROCCO/CALIMA, % Deaths (OCS) = Percentage of deaths during OCS burst (from NRAD), % Deaths (Hosp) = Percentage of deaths during hospital admission (from NRAD).

So, for example, the probability of death during an exacerbation requiring an OCS burst for patients aged 45-100 equals:

$$\text{Probability of death (Hosp) for patients aged } 45-100$$
$$Watson \times \frac{\%\ \text{Exac (Hosp)}\ \ Trial}{\%\ \text{Deaths (Hosp)}\ NRAD} \times \frac{\%\ \text{Deaths (OCS burst)}\ \ NRAD}{\%\ \text{Exac (OCS burst)}\ \ Trial}$$

With numbers:

$$\text{Probability of death during an OCS burst for patients aged } 45-100$$
$$= 0.00383 \times \frac{0.073}{0.3026} \times \frac{0.4667}{0.860} = 0.000501$$

Table 76: Probability of asthma-related death during OCS burst and ER visit (Watson et al. and NRAD)

Age band (years)	Probability of death during OCS burst (Watson et al. + NRAD)	Probability of death during ER visit (Watson et al. + NRAD)
17 - 44	0.000501	0.003165
45 - 100	0.003240	0.020475

The age band 17-44 is used in the DSA and PSA only

Deriving probabilities of death given an exacerbation treated by a hospitalisation

Review of the literature found that Roberts et al. provided a granular (in terms of age) representation of asthma-related mortality following hospital admission for patients (particularly for patients aged 45 years and over). This study investigated the risk of 30-day case fatality following hospitalisation for asthma in adults in Scotland from 1981 to 2009. The Scottish Morbidity Record Scheme with all asthma hospitalisations for adults (>18 years) with ICD9 493 and ICD10 J45-J46 in the principal diagnostic position at discharge was used. These data were linked to mortality data from the General Register Office for Scotland, with asthma case-fatality defined as death within 30 days of asthma admission (in or out of hospital).

Mortality probabilities from the study are outlined in Table 77.

Table 77: Probability of death during hospital admission (Roberts et al. 2013)

Number of deaths (from odds ratio in Roberts et al.)	Age band (years)	Number of hospital admissions (Roberts et al.)	Probability of death during hospital admission (Roberts et al.)
89	45 - 54	19,856	0.00448
210	55 - 64	16,474	0.01275
605	65 - 100	21,779	0.02778

To best model an ageing population, the relative rate ratios of the probabilities for the age bands, 45 – 55, 55 – 64 and 65 – 100 from Roberts et al. were then applied to the Watson et al. 45 –100 band in Table 76. The adjustment assumed that the total asthma admissions were divided equally between the three age categories in order to provide age-stratified probabilities of death following asthma hospital admission for patients with severe asthma (Table 78). This allows for a more granular measurement of asthma related mortality and represents a more conservative estimation than using Watson alone as it allocates the majority of the mortality risk to the later age groups rather than an average across all. This is also in line with the preferred assumption from the mepolizumab NICE STA TA 431.

Table 78: Probability of death following hospital admission (Watson et al. 2007, Roberts et al. 2013)

Age band (years)	Probability of death following hospital admission (Roberts et al.)	Relative rate ratio (Roberts et al.)	Assumption that hospital admissions from Watson et al. are divided equally between the age groups	Deaths following asthma admission (Watson et al.) fitted to relative rate ratios (Roberts et al.)	Probability of death following hospital admission (Watson et al. fitted to Roberts et al.)
45 – 54	0.00448	1	2,381	18	0.00756
55 – 64	0.01275	2.82	2,381	51	0.02142
65 – 100	0.02778	6.18	2,381	108	0.04536

The asthma-specific mortality rates used in the model summarised in Table 79 were applied to the population in the exacerbation states each cycle in proportion to each type of exacerbation Table 75: Percentage of total exacerbations by type.

Table 79: Asthma exacerbation-related mortality inputs used in the base case model

Age band (years)	Probability of death	Data source (Watson et al. 2007, Roberts et al. 2013, NRAD 2014)
OCS burst		
17 – 44	0.000501	Watson et al. + NRAD
45 – 100	0.003240	Watson et al. + NRAD
ER visit		
17 – 44	0.003165	Watson et al. + NRAD
45 – 100	0.020475	Watson et al. + NRAD
Hospital admission		
17 – 44	0.00201	Roberts et al.
45 – 54	0.00756	Watson et al. fitted to Roberts et al.
55 – 64	0.02142	Watson et al. fitted to Roberts et al.
65 – 100	0.04536	Watson et al. fitted to Roberts et al.

The age band 17-44 is used in the DSA and PSA only

The impact of these assumptions is explored in a scenario analysis in Section B.3.8 where asthma related mortality is set to zero.

All-cause mortality

The risk of all-cause mortality was estimated using UK national life-tables for 2012–2014 to apply age- and sex-specific mortality risks to all health states in the model. Asthma-related mortality was not removed from all-cause mortality as the impact of the relatively small number of asthma deaths was considered unlikely to materially impact the results i.e. all patients in all health states experience all-cause mortality, and both all-cause and asthma-related mortality are applied together in the exacerbation states. Table 80 shows the life table used in the model.

Table 80: Life tables

Age	Annual mortality rate		Cycle-length probability of death	
	Male	Female	Male	Female
50	0.003101	0.002156	0.000119	0.000083
51	0.003423	0.002344	0.000132	0.000090
52	0.003702	0.002558	0.000143	0.000099
53	0.004067	0.002780	0.000157	0.000107
54	0.004528	0.002977	0.000175	0.000115
55	0.004865	0.003402	0.000188	0.000131
56	0.005353	0.003674	0.000206	0.000142
57	0.005962	0.004033	0.000230	0.000155
58	0.006607	0.004385	0.000255	0.000169
59	0.007416	0.004772	0.000286	0.000184
60	0.008002	0.005226	0.000309	0.000202
61	0.008809	0.005808	0.000340	0.000224
62	0.009679	0.006283	0.000374	0.000242
63	0.010340	0.006755	0.000400	0.000261
64	0.011306	0.007356	0.000437	0.000284
65	0.012111	0.007936	0.000469	0.000306
66	0.013191	0.008579	0.000511	0.000331
67	0.014606	0.009639	0.000566	0.000372
68	0.016131	0.010748	0.000625	0.000416
69	0.017970	0.011719	0.000697	0.000453
70	0.019796	0.013122	0.000769	0.000508
71	0.022073	0.014429	0.000858	0.000559
72	0.025273	0.016475	0.000984	0.000639
73	0.027243	0.018281	0.001062	0.000709
74	0.029995	0.020211	0.001171	0.000785
75	0.033205	0.022532	0.001298	0.000876

76	0.036573	0.025116	0.001432	0.000978
77	0.040211	0.028226	0.001577	0.001101
78	0.045461	0.031273	0.001788	0.001221
79	0.049611	0.035843	0.001955	0.001403
80	0.056322	0.040816	0.002227	0.001601
81	0.063280	0.045772	0.002511	0.001800
82	0.071519	0.051697	0.002850	0.002040
83	0.079828	0.058965	0.003195	0.002335
84	0.089056	0.067661	0.003581	0.002691
85	0.100248	0.076098	0.004055	0.003040
86	0.111772	0.085623	0.004548	0.003437
87	0.123954	0.096404	0.005077	0.003891
88	0.137712	0.106974	0.005682	0.004342
89	0.152512	0.122022	0.006344	0.004993
90	0.166455	0.136144	0.006978	0.005613
91	0.182981	0.151001	0.007743	0.006276
92	0.208161	0.171558	0.008937	0.007213
93	0.222733	0.185224	0.009644	0.007848
94	0.231918	0.202300	0.010097	0.008656
95	0.259055	0.219153	0.011466	0.009469
96	0.286001	0.251076	0.012873	0.011058
97	0.308416	0.267500	0.014083	0.011901
98	0.330830	0.289642	0.015332	0.013067
99	0.347717	0.315701	0.016299	0.014485
100	0.355920	0.329873	0.016778	0.015278

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

The Phase III clinical trial programme for benralizumab included both a disease-specific quality of life instrument, the AQLQ(S)+12, and a generic preference-based (health utility) instrument, the EQ-5D-5L. The assessment with these instruments across the 3 trials is summarised in Table 81.

Table 81: Quality of Life assessments in the Phase III trial programme

	Study		
Measure	**SIROCCO (48 weeks follow-up)**	**CALIMA (56 weeks follow-up)**	**ZONDA (28 weeks follow-up)**
EQ-5D-5L	Measured weekly / reflects current status		Not measured
AQLQ(S)+12	Measured every 4 weeks / reflects previous 2 weeks.		Measured every 4 weeks / reflects previous 2 weeks.

ER=emergency room; NRAD= National Review for Asthma Deaths; OCS=oral corticosteroid.

The data from the SIROCCO and CALIMA studies, which included both instruments, were pooled and analysed together. Data from ZONDA, which did not include EQ-5D-5L, was analysed separately to map AQLQ(S) +12 to evaluate utility.

Mapping

EQ-5D-5L analysis (POOLED dataset only)

In the base case, in line with a recent position statement by NICE (NICE 2017), the so-called 5L-3L crosswalk value set was used as the method of estimating EQ-5D-3L based utilities. The crosswalk is based on a response mapping approach that estimated the relationship between responses to the EQ-5D-3L ('3L') and EQ-5D-5L ('5L') descriptive systems, and subsequently established a link to the original 3L value set.

For sensitivity analyses, EQ-5D-5L value set was also used to calculate utilities. Devlin et al. recently published a paper outlining an EQ-5D-5L value set for England (Devlin et al. 2017), based on a sample of 996 adult members of the general public, selected at random from residential postcodes between November 2012 and May 2013. The value set is based on a hybrid of the time trade-off and discrete choice approaches.

Mapping of AQLQ(S)+12 to Utility (ZONDA)

Utility estimates from AQLQ(S)+12 based on the ZONDA study were evaluated using a mapping algorithm described by Tsuchiya et al (Tsuchiya et al. 2002). The mapping is based on regressing the EQ-5D-3L index on the AQLQ. The EQ-5D-3L indices used were based on the original UK value set.

Tsuchiya recommends the use of regression model 4, using the coefficients based on the standardised scale (R23 or R123); however, only the coefficients for the individualised scale (R1) are provided (see Appendix 3 of the reference paper).

Model 4 regresses the EQ-5D-3L index on selected AQLQ questions fitted as categorical variables, using the following question based on individualised scale: 1, 3, 5, 6, 25, 26, 27, 29, 31 and 32. Each question in AQLQ has response options from 1 to 7. In model 4, a response of 1 is set as the reference and response 2 through 7 have estimated coefficients. There is also an intercept coefficient. The coefficients will be used to map the AQLQ to an EQ-5D-3L index. A mathematic representation of the model is provided below:

Mapped utility = intercept + β1*Q1 + β3* Q3 + β5*Q5 + β6*Q6 + β25*Q25 + β8*Q26 + β27*Q27 + β31*Q31 + β32*Q32

Where: β* is a 1*6 vector of co-efficients from the fitted model and Q* is a 6*1 vector of indicator variables for responses 2 through 7 for the AQLQ question.

Health-related quality-of-life studies

A systematic literature review was conducted to identify HRQL and utility studies relevant to the decision problem. The databases were searched for HRQL and utility studies. Details of the search strategies are provided in Appendix H

Description of identified studies

The relevant studies identified through the HRQoL/utility SLR are summarised in Table 82.

Table 82: Summary of relevant HRQoL Studies

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Bime 2012 (Bime et al. 2012) US	Adult participants from the SIVA/SARA trials- 1236 participants were included- 137 of which were classed as severe asthma	NR	N=137	ASUI	Severe asthma	0.71 [0.20]
Brown 2007 (Brown et al. 2007) Canada	Subgroup of patients with persistent allergic asthma despite high-dose ICS plus LABA from the ETOPA trial (Ayres et al. 2004)	ICS and LABA	N=117	AQLQ mapped onto EQ-5D	Severe persistent allergic asthma	0.62 (baseline value for 49 patients randomised to standard therapy in the ETOPA trial)
					Severe persistent allergic asthma	0.58 (baseline value for 68 patients randomised to omalizumab in the ETOPA trial)
Brusselle 2009 (Brusselle et al. 2009) Belgium	Patients from the PERSIST trial-with poorly controlled severe persistent allergic asthma despite taking at least an ICS and a LABA	ICS and LABA	N=160	EQ-5D	Severe persistent allergic asthma	0.54 [0.24]
Carroll 2009 (Carroll et al. 2009) US	Adult participants with at least 1 child under the age of 18 years recruited through a Paediatric research network. Parent preferences for paediatric health outcomes were elicited (i.e. not just restricted to asthma-related).	NR	N=350 (severe persistent asthma only)	TTO	Severe persistent asthma (paediatric patients)	0.83 [0.21]
				SG	Severe persistent asthma (paediatric patients)	0.85 [0.20]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Chen 2007 (Chen et al. 2007) US	Patients with severe or 'difficult to treat' asthma from the TENOR study	NR	N=987 (6.6% mild, intermittent or persistent; 39.3% moderate, persistent and 54.4% severe, persistent)	EQ-5D	Severe or 'difficult to treat' asthma	0.86 (0.16)
Dal Negro 2011 (Dal Negro et al. 2011) Italy	Adults with severe difficult to treat asthma (data from respiratory patients attending a general hospital)	NR	N=23	SGRQ mapped to the EQ-5D using a published algorithm (Stahl et al. 2005)	Severe difficult asthma	0.53 (0.18-1)
Dal Negro 2012 (Dal Negro et al. 2012) Italy	Adults with severe uncontrolled atopic asthma on chronic high-dose anti-asthma treatments	Chronic high-dose anti-asthma treatments	N=16	SGRQ mapped to the EQ-5D using a published algorithm (Stahl et al. 2005)	Severe uncontrolled atopic asthma	0.56 [0.22]
Edelen 2008 (Edelen et al. 2008) US	Expert panel methodology to produce interval scale estimates of the average benefit of usual patterns of treatment for asthma	NR	NR	0 to 1 utility scale to establish a common metric. Although the rating scale method does not produce utility estimates under the strictest definition this method was used to minimise the complexity of the task for the expert panellists.	Severe persistent, well controlled	0.738 (range: 0.652-0.851)
					Severe persistent, moderately controlled	0.610 (range: 0.477-0.738)
					Severe persistent, poorly controlled	0.494 (range: 0.249-0.650)

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Ferreira 2010 (Ferreira et al. 2010) Portugal	Patients diagnosed with asthma	NR	N=115 (total population- number of patients with stage IV asthma unclear)	SF-6D	Stage IV asthma (assumed to be severe persistent asthma)	0.86 (0.06)
				EQ-5D	Stage IV asthma (assumed to be severe persistent asthma)	0.75 (0.23)
				EQ-5D-VAS	Stage IV asthma (assumed to be severe persistent asthma)	0.53 (0.16)
Finnell 2012 (Finnell et al. 2012) US	Adult participants with at least 1 child under the age of 18 years. Parent preferences for paediatric health outcomes were elicited (i.e. not just restricted to asthma-related).	NR	N=4016 (number of children with severe asthma unclear)	TTO (TTO first)	Severe persistent asthma	0.82
				SG (TTO first)	Severe persistent asthma	0.84
				TTO (SG first)	Severe persistent asthma	0.87
				SG (SG first)	Severe persistent asthma	0.83
Gunsoy 2016 (Gunsoy et al. 2016) International	Patients with severe eosinophilic asthma from the DREAM trial (Pavord et al. 2012)	NR	N=517	EQ-5D	Severe eosinophilic asthma (total population)	0.73 [0.22]
					Severe eosinophilic asthma (subgroup with not perfect	0.66 [0.19]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
					health at baseline, n=405)	
Levy 2015 (Levy et al. 2015) Spain	Patients aged > 14 years with persistent severe asthma not controlled after > 1 year follow up who had been seen at 4 and 10 months after the initiation of treatment with omalizumab.	NR	N=79	Mini-AQLQ 'mapped' to EQ-5D using a previously published linear model (Chen et al. 2007)	Persistent severe asthma	0.5967 (0.5772-0.6212)
Lloyd 2007 (Lloyd et al. 2007) UK	Patients with a diagnosis of moderate or severe asthma (BTS level 4 or 5) [conducted at four specialist asthma centres].	Patients included were managed with: ≥ 1 high dose ICS combined with any oral or inhaled LABA or any leukotriene-receptor antagonist, or theophylline (Level 4); or, regular oral steroid usage combined with ICS and LABA (Level 5).	N=112	EQ-5D (version not reported) [collected within four weeks of a severe exacerbation managed with OCS and asthma-related hospital admission]	No exacerbation	0.89 [0.15]
					Exacerbation requiring OCS (moderate exacerbation)	0.57 [0.36)
					Exacerbation requiring hospitalisation (severe exacerbation)	0.33 [0.39]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Lloyd 2008 (Lloyd et al. 2008) UK	Members of the public (from which societal preferences for the symptom burden associated with moderate-to-severe asthma was elicited)	NR	N=88	SG	Complete control of moderate-to-severe asthma	0.784 (±0.060)
McTaggart-Cowan 2008 (McTaggart-Cowan et al. 2008) Canada*	Patients with physician diagnosed asthma	NR	N=157	EQ-5D	Severe asthma	0.76 [0.27]
				HUI-3	Severe asthma	0.75 [0.27]
				SF-6D	Severe asthma	0.75 [0.12]
				AQL-5D	Severe asthma	0.74 [0.15]
				EQ-5D VAS	Severe asthma	0.60 [0.25]
				VAS	Severe asthma	0.53 [0.24]
Niven 2016 (Niven et al. 2016) UK (APEX II study)	Patients with severe persistent allergic (IgE-mediated) asthma	Patients were prescribed omalizumab for the first time as part of normal clinical practice (n=22 centres)	N=258	EQ-5D	Severe persistent allergic (IgE-mediated) asthma	*Baseline value for patients by weeks of omalizumab therapy* • 16 weeks, 0.59 [0.25] • 8 months, 0.58 [0.26] • 12 months, 0.58 [0.25]
Norman 2013 (Norman et al. 2013) UK	Patients uncontrolled at step 4, and in the process of moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be	Omalizumab add-on therapy to optimised standard step 4 or 5 GINA therapy	N=NR	EQ-5D	Severe asthma (day to day asthma symptoms used in the model taken from standard care arm)	0.719 [0.026]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
	uncontrolled if they were on step 4 therapy (EXALT trial (Bousquet et al. 2011))	Standard step 4 or 5 GINA therapy				
Pavord 2017 (Pavord et al. 2017) UK	Data obtained from 2010–2011 UK National Health and Wellness Surveys identified 701 patients treated with ICS+LABA (moderate to severe disease severity)	NR	N=701	SF-12	Moderate to severe asthma-not well controlled	0.65
				SF-12	Moderate to severe asthma- well controlled	0.74
				SF-12	Moderate to severe asthma (controlled and not well controlled)	0.69
Steuten 2007 (Steuten et al. 2007) The Netherlands	Patients aged ≥18 years with asthma	NR	N=658 (10% with severe persistent asthma)	EQ-5D	Severe persistent asthma-successful control	0.70 [0.03]
				EQ-5D	Severe persistent asthma-suboptimal control	0.69 [0.04]
				EQ-5D	Severe persistent asthma-GP exacerbation	0.62 [0.03]
				EQ-5D	Severe persistent asthma-hospital exacerbation	0.60 [0.05]

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Suzuki 2017 (Suzuki et al. 2017) Brazil	eXpeRience study (Braunstahl et al. 2013)†: patients with uncontrolled persistent allergic asthma QUALITX study: patients (>12 years) with severe persistent allergic asthma inadequately controlled despite regular treatment with, at least, ICS (≥500 µg/day fluticasone or equivalent) + LABA	eXpeRience study: patients received omalizumab in 'real-world' clinical practice QUALITX study: patients randomised to omalizumab or standard therapy	eXpeRience study: n=37 patients included in utility assessment for standard of care QUALITX study: n=37 patients included in utility assessment for standard of care	AQLQ	Day-to-day asthma symptoms (eXpeRience registry)	0.608
				AQLQ	Day-to-day asthma symptoms (QUALITX study)	0.510
Szende 2009 (Szende et al. 2009) Hungary	Adult asthma patients (from cross-sectional Asthma and COPD HRQOL surveys) [this study was a secondary analysis of these surveys (Szende et al. 2004)]	NR	N=228	EQ-5D	Severe asthma	0.51 [0.16]
				SF-6D	Severe asthma	0.63 [0.10]
Thomson 2013 (Thomson et al. 2013) UK	Patients with severe refractory asthma recruited to the BTS severe asthma registry	NR	N=760	EQ-5D	Never smokers with severe asthma (n=461)	Median 0.7 (IQR 0.5-0.9)
					Ex-smokers with severe asthma (n=210)	Median 0.5 (IQR 0.2-0.7)
					Current smokers with severe asthma (n=69)	Median 0.5 (IQR 0.1-0.7)

Study, Country	Population	Interventions/ comparators	Sample size	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]
Whittington 2017 (Whittington et al. 2017) US	Patients with severe, eosinophilic asthma enrolled in a placebo controlled, phase 3 RCT examining mepolizumab (MENSA) (Ortega et al. 2014)	Patients were randomised to mepolizumab or placebo every 4 weeks for 32 weeks	N=191 randomised to receive placebo (standard therapy)	SGRQ data mapped to EQ-5D using a published mapping algorithm (Starkie et al. 2011) to inform Markov model	Non-exacerbation (standard therapy arm)	0.77
Willson 2016 (Willson et al. 2016) US, Canada, Australia, Germany, UK (Mapping algorithm study)	Patients (≥ 12 years) with severe asthma	NR	N=658	EQ-5D	Severe asthma	0.80 [0.21]

The Lloyd 2007 paper (Lloyd et al. 2007) reports utilities which would fit with the model structure used for this analysis, and as such these values will be considered as a scenario analysis.

Adverse reactions

Across CALIMA and SIROCCO a total of 479 patients were included in the safety set for benralizumab (975 total). Section B.2.10 showed the percentage of subjects experiencing most common on treatment AEs and corresponding events across the placebo controlled severe asthma studies (PCSAs). The integrated safety summary showed that the incidence of AEs was similar for the placebo group (77.6%) compared with the benralizumab (74.7%) group. Nasopharyngitis (19%% in the placebo group and 15% in the benralizumab) and headache (7% in the placebo group and 9% in the benralizumab) were the most frequently reported AEs. The incidence of injection site reactions with benralizumab and placebo was 3% and 3% respectively; all non-serious and the majority resolved in a few days. A total of 15 patients reported AEs leading to withdrawal (0.6% in the placebo group and 2.4% in the benralizumab group). The rate of adverse events observed in the ZONDA trial were similar to those presented above.

Because of these small proportions and minor differences between treatment groups, no adverse events were included in the model.

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

All utility analyses were presented by the following treatment groups:

- Benralizumab 30mg, SC every 8 weeks (Benra 30mg 8w)
- Standard of care (Placebo)

The compound symmetry variance/covariance structure were applied and grouped at the health state level. Least-squares means and standard errors of utility were evaluated at the treatment by health state level. The ZONDA data has limited exacerbations requiring ER or hospitalisations, and therefore only the utility for exacerbations requiring OCS use was assessed. In addition to the modelling approach, summary statistics of the utility values by health states and reporting level were provided by evaluating the mean of the within patient means.

The utility analysis was undertaken separately for each sub-population (base case population, the mepolizumab NICE recommended population and the reslizumab NICE recommended population.

Initially, each patient's utility value was allocated to either the controlled (ACQ<1.5) or uncontrolled (ACQ≥1.5) health state based on the ACQ-6 score measured at the same time as the utility value (for even numbered weeks) or the week following the utility value measure (for odd numbered weeks). This window is based on previous analysis undertaken, which found an exacerbation impacts a patient's utility over the periods outlined below:

- OCS: 24 days prior to exacerbation start data to 24 days post exacerbation start date.
- ER: 31 days prior to exacerbation start data to 31 days post exacerbation start date.
- HOSP: 31 days prior to exacerbation start data to 38 days post exacerbation start date.

To enable the estimates within all the health state specified in Table 83, multiple health state categorisations were required, as specified in Tables 7-27. Each health state categorisation set defines the health state covariate to be used in the repeated measures model. For the POOLED data, Set 1 contains the finest level of health state categorisation. Set 2 and Set 3 collapse selected health state categories from Set 1 together, in order to provide estimates for the collapsed HS categories. The ZONDA HS categorisation sets follow a similar logic to POOLED.

Table 83: Health states category sets, by study

Set 1	Set 2	Set 3
POOLED		
Controlled	Controlled	Controlled
Uncontrolled	Uncontrolled	Uncontrolled
Exacerbation – OCS burst – prior HS controlled	Exacerbation – OCS burst / ER Visit – prior HS controlled	Exacerbation – OCS burst
Exacerbation – ER visit – prior HS controlled		Exacerbation – ER visit
Exacerbation – Hospitalisation – prior HS controlled	Exacerbation – Hospitalisation – prior HS controlled	Exacerbation – Hospitalisation
Exacerbation – OCS burst – prior HS uncontrolled	Exacerbation – OCS burst / ER Visit – prior HS uncontrolled	
Exacerbation – ER visit – prior HS uncontrolled		
Exacerbation – Hospitalisation – prior HS uncontrolled	Exacerbation – Hospitalisation – prior HS uncontrolled	
ZONDA		
Controlled	Controlled	
Uncontrolled	Uncontrolled	
Exacerbation – OCS burst – prior HS controlled	Exacerbation – OCS burst	
Exacerbation – OCS burst – prior HS uncontrolled		

ER=emergency room; HS=health state; OCS=oral corticosteroid.

Table 84 and Table 85 summarise base case utilities for benralizumab and SoC alone arms, by asthma control, exacerbation and mOCS use. For all comparisons with other biologics the utility values within each state are assumed to be the same as those for benralizumab.

Table 84: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Derivation
Controlled, non mOCS, benralizumab	0.8689 (0.01793)	(0.8337572-0.9040428)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population
Controlled, non mOCS, SoC	0.8207 (0.01774)	(0.7859296-0.8554704)	
Controlled, mOCS, benralizumab	0.8478 (0.00907)	(0.8300228-0.8655772)	Mapped EQ-5D-3L values from directly observed AQLQ-12 values in ZONDA trial, base case population
Controlled, mOCS, SoC	0.8562 (0.00994)	(0.8367176-0.8756824)	
Uncontrolled, non mOCS, benralizumab	0.7325 (0.0181)	(0.697024-0.767976)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population
Uncontrolled, non mOCS, SoC	0.7010 (0.0167)	(0.668268-0.733732)	
Uncontrolled, mOCS, benralizumab	0.7364 (0.0165)	(0.70406-0.76874)	Mapped EQ-5D-3L values from directly observed AQLQ-12 values in ZONDA trial, base case population
Uncontrolled, mOCS, SoC	0.6977 (0.01368)	(0.6708872-0.7245128)	
Exacerbation, OCS (burst) prior HS Controlled, non mOCS	0.8209 (0.03732)	(0.7477528-0.8940472)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population
Exacerbation, A+E, prior HS Controlled, non mOCS	0.8209 (0.03732)	(0.7477528-0.8940472)	
Exacerbation, Hospitalised prior HS Controlled, non mOCS	0.6413 (0.05285)	(0.537714-0.744886)	
Exacerbation, OCS (burst) prior HS Controlled, mOCS	0.8189 (0.02638)	(0.7671952-0.8706048)	

Exacerbation, A+E, prior HS Controlled, mOCS	0.8189 (0.02638)	(0.7671952-0.8706048)	Mapped EQ-5D-3L values from directly observed AQLQ-12 values in ZONDA trial, base case population
Exacerbation, Hospitalised, prior HS Controlled, mOCS	0.6413 (0.05285)	(0.537714-0.744886)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population (due to low numbers in ZONDA trial)
Exacerbation OCS (burst), prior HS Uncontrolled, non mOCS	0.7157 (0.02678)	(0.6632112-0.7681888)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population
Exacerbation, A+E, prior HS Uncontrolled, non mOCS	0.7157 (0.02678)	(0.6632112-0.7681888)	
Exacerbation, Hospitalised prior HS Uncontrolled, non mOCS	0.6413 (0.05285)	(0.537714-0.744886)	
Exacerbation, OCS (burst) prior HS Uncontrolled, mOCS	0.6545 (0.01931)	(0.6166524-0.6923476)	Mapped EQ-5D-3L values from directly observed AQLQ-12 values in ZONDA trial, base case population
Exacerbation, A+E prior HS Uncontrolled, mOCS	0.6545 (0.01931)	(0.6166524-0.6923476)	
Exacerbation, Hospital prior HS Uncontrolled, mOCS	0.6413 (0.05285)	(0.537714-0.744886)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population (due to low numbers in ZONDA trial)

HS: health state

The long-term utility loss due to conditions and AEs as a consequence of mOCS use was captured by calculating 2 weekly disutility values from the annual disutility values reported in Sullivan et al (Sullivan et al. 2011). These values were applied by combining data from the ZONDA trial, data provided by the Observational & Pragmatic Research Institute (OPRI) and condition-specific disutility values from Sullivan et al. (Sullivan et al. 2011).

Disutility values of the conditions and AEs listed in the OPRI study (AstraZeneca data on file 2017) were collected from Sullivan et al. (Sullivan et al. 2011) (Table 85). For the majority of conditions and AEs, disutility values of matching disease categories were identified. However, due to a lack of specific estimates for renal impairment and pneumonia, it is assumed that the health effects are comparable to other diseases of kidney and ureters and lung diseases due to external agents respectively, thus the disutility values of 'other diseases of kidney and ureters' and 'lung diseases due to external agents' were assumed to provide proxy estimates.

Table 85: Condition- and AE-specific disutility values

Condition and AE	*Disutility value (Coefficient)*	*Disease categories in Sullivan* et al. *(2011)*
Type 2 diabetes mellitus	0.0621492	CCC049 - diabetes without complications
Osteoporosis	0.0418102	CCC206 - osteoporosis
Glaucoma	0.0278324	CCC088 - glaucoma
Cataract	0.0271471	CCC086 - cataract
Myocardial infarction	0.0556996	CCC100 - acute myocardial infarction
Heart failure	0.1166656	ICD428 - heart failure
Cerebrovascular accident	0.1009164	CCC109 - acute cerebrovascular disease
Renal impairment	0.0963027	CCC 161 - other diseases of kidney and ureters
Peptic ulcer	0.055157	CCC139 - gastroduodenal ulcer (except haemorrhage)
Pneumonia	0.0789687	CCC132 - lung diseases due to external agents

Table 86: Period prevalence or incidence of comorbidities among asthma patients

Daily dose of mOCS (mg)	Type 2 diabetes mellitus	Osteoporosis	Glaucoma	Cataract	Myocardial infarction	Heart failure	Cerebrovascular accident	Renal impairment	Peptic ulcer	Pneumonia
>0 – <0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5 – <2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 – <5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 – <7.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.5 – <15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Disutility values were weighted by the period prevalence and incidence figures for each daily mOCS dose category reported in the OPRI study (Table 86) and by the percentage of patients in each dose category at baseline and at the end of 28 weeks (Table 70). These estimates were combined into an overall disutility value for all mOCS patients for both treatment arms at baseline and at 28 weeks (Table 87).

Table 87: Estimated disutility values of conditions and AEs due to mOCS use

	Benralizumab	Placebo

Daily dose of mOCS (mg)	Baseline	At 28 weeks	Baseline	At 28 weeks
>0 – <0.5	[redacted]	[redacted]	[redacted]	[redacted]
0.5 – <2.5	[redacted]	[redacted]	[redacted]	[redacted]
2.5 – <5	[redacted]	[redacted]	[redacted]	[redacted]
6 – <7.5	[redacted]	[redacted]	[redacted]	[redacted]
7.5 – <15	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]
mOCS – TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

In both benralizumab and standard care arms the overall disutility values were applied as decrements to patients' health state utilities throughout the model's time horizon. Estimated disutility values at baseline were applied to patients using mOCS during the initial 28-week period and estimated disutility values at 28 weeks were applied to patients using mOCS after the initial 28-week period.

This approach is similar to that used in the omalizumab and mepolizumab NICE STAs (National Institute for Health and Care Excellence 2013, NICE 2017) as well as being consistent with advice received during the NICE scientific advice meeting for benralizumab.

The impact of excluding these disutilities is assessed by a scenario analysis in section B.3.8 where the disutilities are set to zero.

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

Resource identification, measurement and valuation studies

A systematic literature review was conducted to identify relevant health costs and resource utilisation costs associated with severe asthma. Please refer to Appendix I for details of the search strategy.

Findings of the SLR are reported in Table 88.

Table 88: Summary of relevant direct cost/resource utilisation studies

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Barnes 2013 (Barnes et al. 2013) UK £, year NR	Payer 1 year (February 2010 to January 2011) Observational cohort	Patients with severe, persistent, allergic asthma (n=136) Definition NR	Data from a retrospective real-world study (data collected from paper and electronic hospital medical records between February 2010 and January 2011) *Mean age at index date, years (SD)* • 41.26 (14.52) *Female, n (%)* • 93 (68.4) *Mean duration of severe allergic persistent asthma, years (SD)* • 26.44 (4.266)	NR	***Mean (SD), per patient per year*** • A&E visits, 1.52 (2.194) • Inpatient hospitalisations, 1.30 (1.731) • No. of bed days, 9.10 (14.438) • Inpatient hospitalisations (n=81/136), 2.19 (1.761) • Bed days for hospitalised subset, 14.86 (16.341) • Respiratory outpatient visits, 6.00 (3.432) • Telephone consultations, 0.23 (0.877) • Nurse consultations, 1.24 (2.209) • Doctor consultations, 1.24 (2.209) • Doctor consultations, 4.54 (3.277) • MDT consultations, 0.06 (0.266)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					• Pharmacist consultations, 0.05 (0.372)
Barry 2017 (Barry et al. 2017) UK £, year NR	Payer Timeframe NR Observational cohort	Patients with severe asthma requiring regular OCS (n=808) **Definition** *Severe:* GINA step 5 treatment and ≥4 prescriptions for OCS in each of two consecutive study years *Mild/ moderate:* treatment at GINA step 2/3	Data obtained from the Optimum Patient Care Research Database. Patients with severe asthma (n=808) matched by age and gender with patients with mild-moderate asthma (n=3975) and a non-asthma control cohort (n=2412) *Mean age at index date, years (SD)* • Severe asthma, 59 (17) • Mild/moderate asthma, 344 (9) • Non-asthma, 58 (17) *Female, n (%)* • Severe asthma, 507 (63) • Mild/moderate asthma, 2515 (63) • Non-asthma, 1481 (61)	**Mean (SD) annual costs** ***Clinical/consultation activity*** *Lowest cost scenario‡* • Severe asthma, £911 (907) • Mild/moderate asthma, £491 (630) • Non-asthma, £350 (546) *Highest cost scenario‡* • Severe asthma, £2,799 (3,705) • Mild/moderate asthma, £1,579 (2,902) • Non-asthma, £1,111 (2,372) ***Prescription drugs*** *Lowest cost scenario‡* • Severe asthma, £1,692 (2,369) • Mild/moderate asthma, £487 (957) • Non-asthma, £210 (790) *Highest cost scenario‡*	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Severe asthma, £1,734 (2,346) • Mild/moderate asthma, £493 (947) • Non-asthma, £212 (700) ***Total direct costs*** *Lowest cost scenario‡* • Severe asthma, £2,603 • Mild/moderate asthma, £978 • Non-asthma, £560 *Highest cost scenario‡* • Severe asthma, £4,533 • Mild/moderate asthma, £2,072 • Non-asthma, £1,324 Unit costs for consultation types were obtained from the PSSRU 2013 (reported in supplementary table 3 of the publication). Adjusted incremental annual non-asthma drug costs (95%	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				CI), severe asthma vs non-asthma control • Female, £789 (652-927) • Male, £744 (620-868) • Total, £772 (641-903)	
Casciano 2016 (Casciano et al. 2016) USA $, year NR	Payer January 2004-July 2011 Retrospective cohort study	Patients aged ≥12 year with a diagnosis of asthma **Definition** *Severe*: based on medication use -ICS + LABA ± OCS (± OCS)	Retrospective analysis of patients with a primary or secondary diagnosis of analysis of asthma using data between January 2004-July 2011 from EMRClaims, an integrated health services database of patients located in the Midwest region of the United States (N=2,164) **Patient characteristics for severe asthma patients (N=179)** *Female, n (%)* • Normal eosinophil levels, 24 (68.6) • Elevated eosinophil levels, 98 (68.1)	***Mean per patient per month cost for severe asthma patients (n=179)*** Outpatient visits: • Normal eosinophil levels, $183 • Elevated eosinophil levels, $203 ER visits: • Normal eosinophil levels, $48 • Elevated eosinophil levels, $37 Admissions: • Normal eosinophil levels, $92 • Elevated eosinophil levels, $201	***Mean per patient per month utilisation for severe asthma patients (n=179)*** Outpatient visits: • Normal eosinophil levels, 1.024 • Elevated eosinophil levels, 0.947 ER visits: • Normal eosinophil levels, 0.130 • Elevated eosinophil levels, 0.100 Admissions: • Normal eosinophil levels, 0.010 • Elevated eosinophil levels, 0.046

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Casciano 2017 (Casciano et al. 2017) USA $, year NR	Payer January 2004-July 2010 Retrospective cohort study	Patients aged ≥12 year with a diagnosis of asthma a **Definition** *Severe*: Based on a) medication use - ICS + LABA or leukotriene modifier or theophylline or b) SCS use greater than 50% of the post-index period (calculated based on days' supply during the 12-month period)	Retrospective analysis of patients with a primary or secondary diagnosis of analysis of asthma using data between January 2004-July 2010 from EMRClaims, an integrated health services database of patients located in the Midwest region of the United States. • Severe asthma, n=216 • Controlled asthma, n=2245 • Uncontrolled asthma, n=456 • Overall, n=2701 Patient characteristics only reported for the controlled and uncontrolled patients	***Mean (SD) total annual cost, per patient*** *Severe asthma* • Normal eosinophil levels, $13,1680 (13,420) • Elevated eosinophil levels, $33,192 (29,161) Data also reported for controlled asthma, uncontrolled asthma and overall asthma	***Mean (SD) total annual admissions, per patient*** *Severe asthma* • Normal eosinophil levels, 0.3 (0.6) • Elevated eosinophil levels, 0.8 (1.6) Data also reported for controlled asthma, uncontrolled asthma and overall asthma
Chastek 2016 (Chastek et al. 2016) US $, 2012 & 2013	Payer January 2012-December 2013 Retrospective cohort study	Patients aged ≥ 12 years who had ≥1 medical claim with an asthma diagnosis in 2012 and had continuous medical and pharmacy coverage under a commercial or	Data taken from a national administrative claims database (from 2012-2013) [n=65,359]. Patients were assigned to 1 of 2 mutually exclusive cohorts—persistent asthma (n=63,597) or severe asthma (n=1,762), according	***Mean unadjusted asthma-related healthcare costs for severe asthma, year 1 (2012)*** • Total costs, $6,496 • Asthma medication, $4,545 • Pharmacy, $1,951 • Hospitalisation, $1,065 • Office visit, $445	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
		Medicare Advantage plan **Definition** *Severe:* patients were required to meet PA criteria and have evidence of ≥2 asthma exacerbations in 2012	to an established algorithm based on asthma-related health care resource use and pharmacy claims for controller medication **Severe asthma patient characteristics (N=1,762)** *Mean age, years (SD)* • 50.8 (16.6) *Male, n (%)* • 604 (64.3)	• Outpatient visit and service, $180 • ER visit, $176 ***Mean unadjusted asthma-related healthcare costs, for severe asthma, year 1 (2013)*** • Total costs, $5,174 • Asthma medication, $4,068 • Pharmacy, $1,106 • Hospitalisation, $548 • Office visit, $329 • Outpatient visit and service, $125 • ER visit, $69 Costs for persistent asthma and unadjusted all-cause health care costs also reported	
Chen 2016 (Chen et al. 2016) Canada $, NR	Payer and Societal Timeframe NR Retrospective matched cohort study	Patients with moderate-to-severe asthma. **Definition** Moderate-to-severe classified on the basis of a validated classification algorithm	Data obtained from the British Columbia's administrative health data for the year 1997-2013 and were matched to adults without asthma on the basis of sex and age	***Mean (95% CI) excess costs of moderate -to-severe asthma*** *Total* • Receiving social assistance, $1,892.1 (1391.8-2,831.7)	***Mean (SD) per patient per year*** • No. of asthma medications 2.1 (3.0)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
			Moderate-to-severe asthma cohort patient characteristics (N=29,283) *Mean age, years (SD)* • 33.9 (8.1 *Male, n (%)* 11,784 (40)	• Not receiving social assistance, $1,186.4 (739.1-1,962.7) • Low level socioeconomic status, $1,292.9 (887.1-2,213.3) • Middle level socioeconomic status, $1,246.2 (798.4-2,251.4) • High level socioeconomic status, $1,173.2 (761.7-2,144.1) Mean excess costs also presented for inpatient, outpatient and medications by socioeconomic status in the publication	
Chen 2016 (Chen et al. 2016) Taiwan NR	Payer 4 months Retrospective, database cohort study	Patients with uncontrolled, persistent allergic asthma (moderate-to-severe predominantly oral steroid dependent asthma) Definition NR	Data obtained from the Taiwan National Health Insurance Research Database (NHIRD) from 2007 to 2011	NR	***Mean (SD) per patient per year*** • ER visits, 1.13 (2.04) • Inpatient visit, 5.93 (16.16)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Chiner 2016 (Chiner et al. 2016) Spain €, 2014	Payer 1 year Retrospective cohort	Patients aged >18 years with severe uncontrolled asthma **Definition** *Severe*: combination maintenance therapy with high-dose ICS and LABA with other drugs, such as oral leukotriene inhibitors and/or long-acting muscarinic antagonists and/or theophylline and/or steroids	Data obtained from two cohorts of patients (in two hospitals), evaluated over a 1-year period (N=130) *Mean age, years (SD)* • 50 (15) *Female, n (%)* • 100 (76)	***Mean cost per patient per year, € (SD)*** • Emergency visits, €484 (737) • Hospitalisation, €1022 (1839) • Pulmonologist consultation, €201 (59) • Primary care consultation, €172 (67)	NR
Dalal 2016 (Dalal et al. 2016) US $,2014	Payer Time frame unclear Retrospective longitudinal open cohort study	Patients aged ≥12 years with ≥2 administrative charges associated with a diagnosis of asthma (severe asthma patients) Definition for severe asthma NR	Data obtained from de-identified claims from the Truven Health MarketScan Research Databases. Collection period between 2003 and 2014. A total of 12,697 CS users identified (and matched 12,697 users also)	***Mean (SD) costs*** • Pharmacy and medical costs, 1,1754 (10,749) • Pharmacy costs, 412 (1,041) • All medical costs, 1,342 (10,672) • Inpatient visit costs, 813 (10,104) • Outpatient visit costs, 337 (2,035) • ER visit costs, 59 (739)	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Other visit costs, 133 (1,337) Data above relates to no CD use, but costs also provided according to CS dose in the publication	
Dal Negro 2012 (Dal Negro et al. 2012) Italy	Payer 36 months Retrospective observational study	Adults with severe uncontrolled atopic asthma on chronic high-dose anti-asthma treatments Definition *Severe*: for Asthma (GINA) guideline definition, resistant to daily high-dose anti-asthma drugs	Data obtained from an institutional database, N=16. *Mean age, years (min, max)* • 45.4 (31, 64) *Female, n (%)* • 8 (50)	NR	***Mean (SD) per patient per year*** • Hospitalisations per year, 0.94 (0.68) • Emergency unit accesses, 0.69 (0.95) • GP visits, 3.38 (2.03) • Specialist visits, 2.06 (1.24)
Darba 2016 (Darba et al. 2016) Spain €, 2015	Payer 4-year Budget impact analysis	Patients with moderate-to-severe asthma Definition NR	The use of health care resources was estimated based on data from clinical practice by consulting a panel of five clinical experts in pneumology, allergy, and a general practitioner from several Spanish hospitals. Collection period NR.	***Total healthcare cost per patient per year*** • Drug cost, €221 • Cost of medical visits, €405 • Cost of hospital resource utilization, €5 • Cost of other interventions, €138 • Cost per patient, €769	***Mean per patient per year*** *Medical visits* • Primary care visits, 4.80 • Specialist physician visits, 2.00 • Emergency visits, 0.014

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					• Hospitalisations, 0.003 • Days of length of stay, 3.60 • Number of spirometries, 3.5
del Carmen Vennera 2016 (del Carmen Vennera et al. 2016) Spain €, 2016	Societal 1 year Cost-effectiveness study	Patients with severe persistent allergic asthma uncontrolled by standard treatment for ≥12 months Definition NR	Data were collected from medical record review of 86 uncontrolled severe persistent asthma patients treated with omalizumab between January 2005 to April 2014. *Mean age, (SD)* • 50.57 (13.63) *Male, n (%)* • 29 (40.8) *Mean duration of asthma, years (SD)* • 24.82 (15.39)	**Annual cost per patient (95% CI)** • Exacerbation without ER visit or hospitalisation, €292.25 (254.59, 337.28) • Exacerbation with ER visit, €894.75 (790.05, 1,016.11) • Exacerbation with hospital admission, €996.27 (591.53, 1,494.40) • Drug cost, €1,818.48 (1,636.12, 2,023.44) • Total drug costs, €4,001.75 (3,472.36, 4,674.55) • Annual cost per patient (95% CI), €8,052.34 (7,122.11, 8,974.53)	NR
Dilokthornsakul 2016	Payer	Asthma patients receiving care from a	Data obtained from a Thai hospital electronic database; data were collected for	***Annual mean (SD) cost, per patient***	***Annual mean (SD), per patient***

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
(Dilokthornsakul et al. 2016) Thailand $, 2011	3 years Observational cohort	university-affiliated hospital in Thailand. **Definition** *High severe group*: patients who received SABAs >13 times or received oral steroids >2 times and received SABA 5-13 times in a past year	patients diagnosed with asthma between January 2009 and December 2011 (N=1982). Patient characteristics not reported for the high severe group of patients only (n=46)	• Total medical cost, $658 (414) • Total medical outpatient cost, $537 (373) • Outpatient drug cost, $454 (355) • Other outpatient costs, $82 (92) • Total medical inpatient cost, $121 (261) • Inpatient drug cost, $10 (30) • Inpatient other cost, $110 (238) ***Mean (95% CI) additional annual health care cost relative to mild/moderate severe disease*** • High severe, $71 (131-274) Outcomes also reported for all patients and the mild/moderate severe group	• Outpatient visits (times), 10.78 (4.33) • Inpatient visits (times), 0.30 (0.55) ***Mean (95% CI) incidence rate ratio of hospitalisation relative to mild/moderate severe disease*** • High severe, 1.33 (0.63-2.82)) Outcomes also reported for all patients and the mild/moderate severe group
Ivanova 2012 (Ivanova et al. 2012)	Payer 1 year	Patients aged 12-62 years with an asthma diagnosis	Data for patients with moderate-to-severe asthma were obtained from a claims database covering more than	***Annual mean (SD) cost, per patient*** *Total direct costs*	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
US $, 2007	Observational	**Definition** *Severe persistent*: receiving medium or high dose ICS + LABA with other controllers *Moderate persistent*: receiving low dose ICS and either a LABA, LM or theophylline or medium or high dose IC	8 million privately insured beneficiaries from 40 US based companies for 1997-2007. • Moderate/severe persistent asthma with ≥1 exacerbation (N=3,830) • Moderate/severe persistent asthma with no exacerbations (N=3830) *Mean age, years (SD)* • Moderate/severe persistent asthma with ≥1 exacerbation, 40.09 (15.43) • Moderate/severe persistent asthma with no exacerbations, 39.93 (15.49) *Male, n (%)* • Moderate/severe persistent asthma with ≥1 exacerbation, 1,444 (37.7)	• Patients with moderate/severe asthma with ≥1 exacerbation, $7,047 (19,841) • Patients with moderate/severe asthma without exacerbations, $4,849 (7,811) *Asthma-related direct costs* • Patients with moderate/severe asthma with ≥1 exacerbation, $1,221 (2,337) • Patients with moderate/severe asthma without exacerbations, $947 (1,289)	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
			• Moderate/severe persistent asthma with no exacerbations, 1444 (37.7)		
Kerkhof 2017 (Kerkhof et al. 2017) UK £, 2015	Payer (UK NHS) 1 year Historical cohort	Patients aged ≥5 years with severe, uncontrolled, eosinophilic asthma (SUEA) **Definition** *Severe*: combination maintenance therapy with high-dose ICS and LABA in both the baseline and outcome years *Uncontrolled:* ≥2 asthma attacks in the baseline year *Eosinophilic asthma*: blood eosinophil count of ≥0.3 X 10^9/L at index date	Data obtained from the Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD)† December 1989 to June 2015 *Female* • All asthma patients, (n=363,558), 64.1% • SUEA, (n=2,940), 66.4% *Age at index date, years (SD)* • All asthma patients, 49.4 (20.6) • SUEA, (n=2,940), 55.8 (17.6)	***Mean (SD) [median, IQR], per patient per outcome year*** *GP† visits* • All asthma patients, £30.8 (49.8) [£14.5, 0.0-43.4] • SUEA, £77.0 (107.5) [£44.0, 14.5-101.7] *Hospital-based specialist visits* • All asthma patients, £6.90 (52.2) • SUEA, £46.7 (149.2) *Asthma-related ED attendances* • All asthma patients, £1.60 (18.8) • SUEA, £6.60 (44.7) *Hospitalisations* • All asthma patients, £10.40 (194.7)	***Mean (SD) [median, IQR], per patient per outcome year*** *No. of GP† visits* • All asthma patients, 1.36 (1.57) [1, 0-68] • SUEA, 2.67 (2.80) [2,0-36] *No. of hospital-based specialist visits* • All asthma patients, 0.04 (0.33) [0, 0-12] • SUEA, 0.30 (0.96) [0, 0-12] *No. of asthma-related ED attendances* • All asthma patients, 0.01 (0.11) [0, 0-6] • SUEA, 0.04 (0.25) [0, 0-15]

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• SUEA, £78.70 (660.3) *Medication cost* • All asthma patients, £170.1 (218.2) [£87.8, 18.0-24.9] • SUEA, £645.4 (285.4) [£595.3, 451.8-760.5] *Total direct costs* • All asthma patients, £222.0 (337.2) [£125.6, 43.1-297.9] • All asthma patients with concomitant COPD, £530 • SUEA, £861.0 (811.9) [£707.0, 523.0-951.0] • SUEA with concomitant COPD, £866 Data also reported for the subset of patients receiving maintenance OCS during the baseline year (n=10,552)	*No. of hospitalisations* • All asthma patients, 0.01 (0.12) [0, 0-12] • SUEA, 0.05 (0.38) [0, 0-9] Asthma-related resource use was shown to increase with an increasing blood eosinophil count Data also reported for the subset of patients receiving maintenance OCS during the baseline year (n=10,552)
Kim 2012 (Kim et al. 2012) South Korea	Payer and societal 1 year	Adult patients aged >14 years with persistent asthma **Definition**	Data obtained from eight tertiary hospitals participating in the cohort for Reality and Evolution of Adult Asthma study in the Seoul and	***Mean cost, per patient per year*** • Direct costs, $2213.9 • Official medical cost, $1,791.2	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
$, 2009	Retrospective cohort	Severity of asthma as per GINA • *Mild:* asthma that could be well controlled with low-intensity GINA step 2 treatment such as low-dose ICS or leukotriene modifiers • *Moderate*: well-controlled asthma with GINA step 3 treatment • *Severe*: asthma requiring high-intensity treatment such as GINA step 4 or 5 to maintain good control or where good control was not achieved despite high-intensity treatment	Gyeonggi provinces of Korea (N=314). **Severe asthma patient characteristics** *Mean age, years* • 61.2 *Male, n (%)* • 40 (35.5)	• Hospital cost, $964.9 • Outpatient medication cost, $826.3 • Nonofficial medication cost, $297.7 • Oriental medicine, $49.9 • Alternative medicine, $243.0 • Other instruments, $6.3 • Non-medical direct cost, 126.0 [Percentages per total costs for which the individual is responsible are also reported in the publication] ***Mean cost, per patient per year for severe asthma patients according to control status*** • Well controlled, $1119.7 • Somewhat controlled, $1230.4 • Poorly controlled, $2439.4	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				Indirect costs also reported in the publication	
Lee 2017 (Lee et al. 2017) South Korea $, 2014	Payer 1 year Retrospective cohort	Adult patients with asthma and ≥2 claims for an asthma diagnosis; patients were prescribed ≥ 1 medication **Definition** Severity of asthma as per GINA: • *Level 1 (mild):* patients using ≥1 asthma medication (except ICS + LABA), N=29,785 • *Level 2 (moderate):* patients prescribed the combination therapy of ICS + LABA, N=6670 • *Level 3 (severe):* patients treated with the combination of an ICS, LABA, and low-dose oral CS for ≥2 weeks, N=232	Data obtained from health insurance claims database between January and December 2014 (N=36,687) **Severe asthma patient characteristics (N=232)** *Mean age, years (SD)* • 65.9 (14.6) *Female, n (%)* • 109 (47.0)	***Annual asthma-related costs and acute exacerbation costs per patient with severe asthma, $ (SD)*** • All patients, $1635 ○ ED visit, 13 (0.8) ○ Hospitalisation, 835 (51.0) • Patients without exacerbation, $873 • Patients with ≥1 exacerbation, $2,438 • CS burst, $210 • ED visit, $201 • Hospitalisations, $201 ***Annual total cost (asthma related costs and acute exacerbation costs) per patient with severe asthma, $ (SD)*** • Exacerbation cost, $154,760 (40.8)	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Lefebvre 2015 (Lefebvre et al. 2015, Lefebvre et al. 2015) US $, 2013	Payer Timeframe NR Observational cohort	Eligible patients were ≥12 years with ≥2 severe asthma diagnoses and had more than 6 months of continuous SCS use Definition NR	Data from health insurance claims database (1997-2013: Medicaid), N=3,628. 1997-2013 *Mean age, years (SD)* • 57.6 (16.3) *Female, n (%)* • 2,478 (68.3)	**Annual index data costs, mean (SD)** • All-cause health care costs, $18,142 (28,668) • Asthma-related total medical costs, $1,862 (7,066) **Annual unadjusted healthcare costs by SCS-related exposure, mean (SD)** *Pharmacy and medical costs* • Low SCS exposure, $2,515 ($5,528) • Medium SCS exposure, $3,342 ($6,149) • High SCS exposure, $4,465 (8,254) *Pharmacy costs* • Low SCS exposure, $674 ($1,534) • Medium SCS exposure, $1,028 ($1,711) • High SCS exposure, $1,336 (2,143) *All medical costs*	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Low SCS exposure, $1,840 ($5,081) • Medium SCS exposure, $2,314 ($5,658) • High SCS exposure, $3,129 (7,804) *Inpatient visit costs* • Low SCS exposure, $571 ($2,800) • Medium SCS exposure, $881 ($3,818) • High SCS exposure, $1,324 (5,125) *Outpatient visit costs* • Low SCS exposure, $384 ($2,951) • Medium SCS exposure, $485 ($2,654) • High SCS exposure, $881 (4,813) *ED visit costs* • Low SCS exposure, 6 ($32) • Medium SCS exposure, $9 ($44) • High SCS exposure, $12 (18)	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				Other visit costs • Low SCS exposure, 880 ($2,742) • Medium SCS exposure, $939 ($3,058) • High SCS exposure, $911 (3,104) Incremental costs versus no SCS exposure reported in Lefebvre 2017 (Lefebvre et al. 2017)	
Menzella 2012 (Menzella et al. 2012) Italy €, NR	Payer 4 years Retrospective observational study	Patients aged 12-75 years with severe allergic asthma Definition NR	Patients were originally enrolled as part of an international multicentre, open-label, parallel- group clinical trial (N=11) *Mean age, years (SD)* • 47.5 (9.64) *Female, n (%)* • 6 (36.4)	**Costs per patient per year** • Hospitalisation, €2,158 • ED cost, €73 • Exacerbation, €211 • Total drugs cost €1,858 • Total costs, €4,027	NR
Niven 2016 (Niven et al. 2016)	Payer (NHS secondary care centres)	Patients (aged 16 years or over) with severe persistent allergic (IgE-mediated) asthma for	Retrospective data for the 12-month pre-omalizumab period for each patient were collected from paper-based	NR	**Mean resource utilisation (SD) per patient**

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
UK (APEX II study) £, 2015	1 year Retrospective medical review	whom omalizumab was prescribed for the first time as part of normal clinical practice in NHS secondary care centres Definition NR	and electronic medical records. • Mean age (SD), 44.7 years (14.2) • Female, 65.1%)		• A&E visits, 1.12 (0.91) • Inpatient admissions, 1.24 (1.64) • Outpatient visits, 4.60 (2.48) • Bed days, 6.61 (9.73) • Day case visits, 0.03 (0.18)
Ojeda 2013 (Ojeda et al. 2013) Spain €, 2011	Payer and societal 3 Seasons Observational epidemiological study	Patients aged 18-65 years with a confirmed diagnosis of asthma based on the GINA criteria Definition NR	120 allergists worldwide were asked to select asthmatic patients aged 18 to 65 years who were evenly distributed according to the 4 levels of asthma severity (GINA) during three different seasons. N=1186 patients enrolled February-November 2010 *Asthma severity, n (%)* • Intermittent, 274 (25.1) • Mild persistent, 294 (26.9)	Direct annual costs for severe persistent asthma, €2,921.63	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
			• Moderate persistent, 299 (27.4) • Severe persistent, 226 (27%)		
O'Neill 2015 (O'Neill et al. 2015) UK £, 2012	Payer 1 year Observational economic analysis	Patients were characterised as having severe, refractory asthma using systematic evaluation protocols Definition NR	Data obtained from the BTS National Registry for dedicated UK Difficult Asthma Services in 2012§ (N=516). *Mean age, years (SD)* • 48.5 (13.9) *Female, %* • 62%	***Mean (SD) annual costs for severe refractory asthma:*** • Unscheduled GP or A&E visits, £466 (372) • Scheduled GP or A&E visits, £175 (140) • Unscheduled hospital visits, £848 (1440) • Scheduled hospital visits, £588 (0) • Total non-medication related costs, £2,077 (1,644) • Total medication related costs, £2,139 (1,578) • Total cost, £4,217 (2,449) • Total asthma medication costs, £1,705 (1,417) High cost scenario data extracted, but low-cost scenario data also reported in the publication together with a detailed breakdown of	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				medication costs (full details of the high and low-cost scenarios are provided in the publication supplementary appendix)	
Pavord 2017 (Pavord et al. 2017) UK, 2001 £, NR	Payer and societal Timeframe unclear Observational	Patients who self-reported a physician diagnosis of asthma and taking either a fixed-dose or free combination of ICS and LABA for their asthma. Definition NR	Data obtained from 2010–2011 UK National Health and Wellness Surveys identified 701 patients treated with ICS+LABA (moderate to severe disease severity). N=701	***Mean costs per person*** *Physician visits* • Not-well controlled, £551 • Well-controlled, £375 *A&E department visits* • Not-well controlled, £95 • Well-controlled, £60 *Hospitalisations* • Not-well controlled, £708 • Well-controlled, £322 *Direct costs* • Not-well controlled, £1,355 • Well-controlled, £758 *Absenteeism* • Not-well controlled, £2,747 • Well-controlled, £1,012 *Presenteeism* • Not-well controlled, £4,480 • Well-controlled, £2,181 *Total costs (includes indirect costs)* • Not-well controlled, £6,592	***Mean, per patient during previous 6 months*** *No. of GP visits* • Not-well controlled, 3.6 • Well-controlled, 2.3 • All patients, 3.1 *No. of specialist visits* • Not-well controlled, 4.1 • Well-controlled, 2.8 • All patients, 3.6 *No. of A&E department visits* • Not-well controlled, 0.13 • Well-controlled, 0.07 • All patients, 0.11 *No. of hospitalisations* • Not-well controlled, 0.22 • Well-controlled, 0.14 All patients, 0.19

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				Well-controlled, £3,220	
Plaza-Martin 2014 (Plaza-Martin et al. 2014) Spain NA	Payer 3 months Observational study	Patients aged 6-14 years having spirometry performed in the previous six months, and diagnosis of severe asthma according to the physicians' criteria. Definition NR	Data from 30 Spanish hospitals were collected over a period of 3 months (N=207) *Mean age, years (SD)* • Controlled severe asthma patients, 11.5 (2.1) • Difficult to control severe asthma patients, 10.4 (2.3) *Male, n (%)* • Controlled severe asthma patients, 37 (54.3) • Difficult to control severe asthma patients, 90 (65.0)	NR	***Annual mean (SD), per patient*** *No. of hospitalisations* • Controlled severe asthma patients, 0.1 (0.3) • Difficult to control severe asthma patients, 0.4 (1.1) *Number of ER visits* • Controlled severe asthma patients,1.0 (1.3) • Difficult to control severe asthma patients, 2.4 (3.3) *No. of unscheduled primary care visits* • Controlled severe asthma patients, 1.9 (2.1) • Difficult to control severe asthma patients, 4.4 (3.9)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Smith 2012 (Smith et al. 2012) UK £, 2007-2008	Payer 1 year Randomised cluster trial	Patients with severe asthma aged ≥5 years **Definition** *Severe:* In the last 2 years, medications approximating to BTS Step 4-5 or asthma admission in the last 5 years or A&E visit for asthma in the last year or Brittle asthma	Patient data were extracted electronically from practice-based computerised records. Data were collected for the 1 year prior to activation of the intervention (electronic alerts to flag patients' at-risk status) and for the 1-year period following intervention (N=911) *Mean age, years (SD)* • 45.5 (21.9) *Female, n (%)* • 558 (61.3)	***Mean annual costs (at baseline)*** *Primary care* • Intervention, £305.28 • Control, £299.54 *Secondary care* • Intervention, £923.81 • Control, £1023.13 *Out of hours* • Intervention, £21.29 • Control, £31.67 *Medication* • Intervention, £879.45 • Control, £866.33 *Total cost* • Intervention, £2129.83 • Control, £2220.68 Respiratory or non-respiratory related costs also reported in the publication	***Mean annual number of contacts/prescriptions (at baseline)*** *Primary care* • Intervention, 11.88 • Control, 11.66 *Secondary care* • Intervention, 3.51 • Control, £3.38 *Out of hours* • Intervention, 0.52 • Control, 0.81 *Medication* • Intervention, 64.26 • Control, 59.68 Respiratory or non-respiratory resource use also reported in the publication

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Sullivan 2015 & 2015b (Sullivan et al. 2015, Sullivan et al. 2015) US $, 2011	Payer 1 year Before versus after retrospective cohort study	Patients aged 12-75 years with asthma newly initiated to omalizumab high intensity CS or high dose ICS (severe asthma) Definition NR	Data were obtained from the 2002-2011 MarketScan Commercial Claims and Encounters Database. N=19,227, newly initiated to: • Omalizumab, n=856 • High intensity CS, n=6,926 • High dose ICS, n=11,445 *Male, n (%)* • Omalizumab, 331 (39) • High intensity CS, 2,388 (34) • High dose ICS, 4,261 (37)	**Mean unadjusted annual asthma-related expenditures at baseline** *Health care cost* • High dose ICS, $1,511 • High intensity CS, $2,637 • Omalizumab, £4,712 *Prescription cost* • High dose ICS, $594 • High intensity CS, $1,022 • Omalizumab, £1,693 *Medical cost* • High dose ICS, $917 • High intensity CS, $1,615 • Omalizumab, £3,019 *Outpatient cost* • High dose ICS, $403 • High intensity CS, $529 • Omalizumab, £2,051 *Inpatient cost* • High dose ICS, $448 • High intensity CS, $987 • Omalizumab, £824 *ED cost* • High dose ICS, $66	**Mean (SE) annual asthma related health resource use at baseline** *Outpatient visits* • High dose ICS, 2.10 (0.03) • High intensity CS, 2.59 (0.05) • Omalizumab, 7.40 (0.38) *Inpatient visits* • High dose ICS, 0.04 (0.00) • High intensity CS, 0.07 (0.00) • Omalizumab, 0.09 (0.01) *Inpatient length of stay* • High dose ICS, 0.11 (0.01) • High intensity CS, 0.27 (0.02) • Omalizumab, 0.26 (0.05) *ED visits*

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• High intensity CS, $99 • Omalizumab, £145 *Speciality care cost* • High dose ICS, $92 • High intensity CS, $122 • Omalizumab, £810 Total (not asthma-specific) expenditures also reported in the publication	• High dose ICS, 0.10 (0.00) • High intensity CS, 0.15 (0.01) • Omalizumab, 0.20 (0.02) *Urgent care visits* • High dose ICS, 0.01 (0.00) • High intensity CS, 0.01 (0.00) • Omalizumab, 0.00 (0.00) *Home health visits* • High dose ICS, 0.05 (0.01) • High intensity CS, 0.10 (0.01) • Omalizumab, 0.20 (0.04) *Regular office visits* • High dose ICS, 0.87 (0.01) • High intensity CS, 0.95 (0.02) • Omalizumab, 1.08 (0.11)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					Speciality care visits • High dose ICS, 0.62 (0.02) • High intensity CS, 0.82 (0.03) • Omalizumab, 1.08 (0.11) *Prescriptions (n)* • High dose ICS, 5.17 (0.06) • High intensity CS, 7.80 (0.09) • Omalizumab, 11.74 (0.34) Total (not asthma-specific) health resource utilisations also reported in the publication
Thomson 2013 (Thomson et al. 2013) UK £, NR	Payer and societal Time frame NA Observational	Patients with severe refractory asthma **Definition** Severe: as per the American Thoracic Society criteria for severe asthma	Patients with severe refractory asthma recruited to the BTS severe asthma registry (N=760) • Never smoked with severe asthma (n=461)	NR	***Mean (IQR) resource use in the last year*** *Unscheduled GP/A&E visits* • Never smoked with severe asthma, 4 (2-6)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
			• Ex-smokers with severe asthma (n=210) • Current smokers with severe asthma (n=69) *Mean age, years (SD)* • Never smoked with severe asthma, 43 (14) • Ex-smokers with severe asthma, 49 (12) • Current smokers with severe asthma, 42 (10) *Female, n (%)* • Never smoked with severe asthma, 316 (69) • Ex-smokers with severe asthma, 114 (54) • Current smokers with severe asthma, 50 (73)		• Ex-smokers with severe asthma, 4 (2-7) • Current smokers with severe asthma, 6 (3-8) *Hospitalisations* • Never smoked with severe asthma, 0 (0-13) • Ex-smokers with severe asthma, 0 (0-14) • Current smokers with severe asthma, 0 (0-12) *ITU admissions (ever)* • Never smoked with severe asthma, 0 (0-12) • Ex-smokers with severe asthma, 0 (0-4) • Current smokers with severe asthma, 0 (0-20)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Willson 2014 (Willson et al. 2014) UK £, 2012	Payer Timeframe NR Cost-effectiveness study	The PrimoTinAasthma® clinical trials recruited asthma patients. **Definition** Asthma patients who were Poorly controlled, confirmed by an ACQ7 score ≥1.5 despite usual care comprising at least a high-dose ICS/LABA. Patients were also assumed to receive high-dose ICS/LABA as controller therapy	Data obtained from the PrimoTinAasthma® trial database. Collection period NR. Patient characteristics NR	**Inpatient resource use (cost per episode)** • Asthma-related hospitalisations, £785.98 • Severe exacerbation-related hospitalisation, £1,524.28 • A&E visit only, £108.22 • A&E + hospitalisation, £1,691.49 • Ambulance + hospitalisation, £1,763.93 • Ambulance + hospitalisation + A&E visit, £1,927.15 • Hospitalisation including ICU stay, £2,242.45 **Outpatient visit resource use (cost per episode)** • Visit to GP, £43 per visit • Visit to Nurse, £13.69 per visit • Visit to Respiratory Specialist, £133.26 per visit • Visits from GP, £110.00 per visit v) Visit from nurse, £37.33 per visit	Controlled Asthma (per week): • Asthma-related hospitalisation 0.0034 • Visits to GP, 0.031 • Visits to nurse, 0.050 • Visits to respiratory specialist, 0.016 • Visits from GP, 0.00082 • Spirometry test, 0.026 • Flu vaccine, 0.020 • Desensitisation, 0.0046 Partially Controlled Asthma (per week): • Asthma-related hospitalisation, 0.0038 • Visits to GP, 0.039

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				Laboratory test costs • Spirometry test, £28.20 • Flu vaccine, £6.32 • Desensitisation, £175.32 **Total weighted cost per week** • Controlled asthma: £7.18 • Partly-controlled asthma, £11.61 • Uncontrolled asthma, £41.80 • Non-severe exacerbation: £65.58 5 • Severe exacerbation with hospitalisation: £83.50	• Visits to nurse, 0.068 • Visits to respiratory specialist, 0.033 • Visits from GP, 0.0095 • Spirometry test, 0.028 • Flu vaccine, 0.020 • Desensitisation, 0.0077 Uncontrolled Asthma (per week) • Asthma-related hospitalisation, 0.0061 • Visits to GP, 0.014 • Visits to nurse, 0.16 • Visits to respiratory specialist, 0.094

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					• Visits from GP, 0.025 • Visits from nurse, 0.00072 • Spirometry test, 0.049 • Flu vaccine, 0.02 • Desensitisation, 0.0087 Non-severe Exacerbation (per week) • Visits to GP, 0.6 • Visits to nurse, 0.43 • Visits to respiratory specialist, 0.094 • Visits from GP, 0.034 • Spirometry test, 0.29 Severe Exacerbation without hospitalisation (per week • A&E visit only, 0.58

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					• Visits to GP, 1.37 • Visits to nurse, 0.9 • Visits to respiratory specialist, 0.34 • Visits from GP, 0.22 • Visits from nurse, 0.0033 • Spirometry test, 0.29 Severe Exacerbation with hospitalisation (per week) • Severe exacerbation-related hospitalisation, 0.39 • A&E visit & hospitalisation, 0.41 • Ambulance & hospitalisation, 0.022

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
					• Ambulance & A&E & hospitalisation, 0.043 • Hospitalisation including ICU stay, 0.13 • Visits to GP, 0.59 • Visits to nurse, 1.38 • Visits to respiratory specialist, 1.76 • Visits from GP, 0.102 • Visits from nurse, 0.0047 • Spirometry test, 0.46
Zeiger 2016 (Zeiger et al. 2016) US	Payer 1 year Observational	Patients aged ≥12 years who has persistent asthma in the baseline year (2012). **Definition**	Data obtained from administrative databases (Kaiser Permanente Southern California research data warehouse).	***Mean annual costs (SD) for severe uncontrolled asthma*** *All-cause* • Total, $4800 (185)	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
$, 2013		*Severe uncontrolled asthma*: ≥ 2 asthma exacerbations; ≥6 medium or high dose ICS canisters dispensed as monotherapy or in combination with LABA and ≥3 non-ICS controller canisters dispensed	• Persistent asthma cohort, N=23,935 • Severe uncontrolled asthma, N=585 • Non-severe uncontrolled asthma, N=25,350 Patient characteristics for the severe, uncontrolled cohort: *Mean age, years (SD)* • 50.6 (16.9) *Female, n (%)* • 372 (63.6)	• Hospitalisation including laboratory and radiology, $1043 (141) • ED including laboratory and radiology, $1043 (141) • Outpatient visits including laboratory and radiology, $1235 (41) • Asthma drug (non-asthma drugs not captured), $2007 (56) • Laboratory, $93 (7) • Other (radiology, skilled nursing, hospital outpatients and home health, $191 (36) *Asthma-related* • Total, $2325 (75) • Hospitalisation including laboratory and radiology, $171 (51) • ED including laboratory and radiology, $21 (4) • Outpatient visits including laboratory and radiology, $133 (8) • Asthma drug, $2007 (56)	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
Zeiger 2017 (Zeiger et al. 2017) US $, 2014	Payer 1 year Observational cohort	Adults aged 18-64 years with persistent asthma **Definition** Severe asthma patients not explicitly defined but assumed to be those patients classed as GINA step-care level 4 or 5 (N=400)	Data obtained from administrative databases (Kaiser Permanente Southern California research data warehouse). Data collected from patients with persistent asthma with blood eosinophil determination in 2009 and 2010 (N=2,392). Patient characteristics NR	***Mean (SD) annual direct costs in 2010 for patients with ≥1 asthma exacerbation*** *Total all-cause costs for step-care level 4 or 5 patients* • Total, $7,086 (7,264) • Inpatient visits, $2,051 (5,725) • Hospital outpatient visits, $148 (544) • ED visits, $258 (357) • Outpatient visits, $2048 (2,557) • Laboratory, $99 (164) • Radiology, $91 (210) • Asthma medication, $2,477 (1,875) *Total asthma-related costs for step-care level 4 or 5 patients* • Total, $3,843 (3,432) • Inpatient visits, $387 (1,938) • Hospital outpatient visits, $6 (99) • ED visits, $29 (129)	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Outpatient visits, $585 (987) • Asthma medication, $2,477 (1875) ***Mean (SD) annual direct costs in 2010 for patients with 2 or more asthma exacerbations*** *Total all-cause costs for step-care level 4 or 5 patients* • Total, $7,430 (7,004) • Inpatient visits, $2,204 (5,839) • Hospital outpatient visits, $163 (569) • ED visits, $203 (398) • Outpatient visits, $2058 (1,606) • Laboratory, $88 (152) • Radiology, $84 (187) • Asthma medication, $2,630 (1,917) *Total asthma-related costs for step-care level 4 or 5 patients* • Total, $4,107 (4,051)	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Inpatient visits, $689 (2,576) • Hospital outpatient visits, $13 (155) • ED visits, $54 (184) • Outpatient visits, $720 (803) • Asthma medication, $2,630 (1917)	
Zeiger 2017b (Zeiger et al. 2017) US $, NR	Payer 1 year Prospective observational study	Patients aged ≥12 years who had severe uncontrolled asthma in the baseline year (2012) **Definition** *Severe uncontrolled asthma*: ≥ 2 asthma exacerbations; ≥6 medium or high dose ICS canisters dispensed as monotherapy or in combination with LABA and ≥3 non-ICS controller canisters dispensed	Patients were identified from Zeiger 2016 (Zeiger et al. 2016) and invited to participate in this prospective follow-up study (N=261) *Mean age, years (SD)* • 52.1 (16.1) *Female, n (%)* • 174 (66.7)	***Mean annual unadjusted direct costs in 2013 for patients with severe uncontrolled asthma related to blood eosinophil cut-off points*** *Costs for eosinophil ≥ 300 cells/mm^3 (n=101)* • Total, $5,155 (3,786) • Inpatient visits, $819 (2,698) • Hospital outpatient visits, $142 (400) • ED visits, $106 (283) • Outpatient visits, $1,437 (1,164) • Laboratory, $99 (205) • Radiology, $74 (138)	NR

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Asthma medication, $2,473 (1,805) • Home health, $5.0 (40) *Asthma-related costs for eosinophil ≥ 300 cells/mm³ (n=101)* • Total, $3,030 (2,195) • Hospital, $119 (691) • ED, $39 (142) • Outpatient: uncontrolled asthma, $157 (229) • Outpatient: controlled asthma, $243 (315) • Asthma medication, $2,473 (1,805) *Total all-cause for eosinophil < 300 cells/mm³ (n=160)* • Total, $6,025 (4,891) • Inpatient visits, $1,039 (3,533) • Hospital outpatient visits, $127 (375) • ED visits, $96 (247) • Outpatient visits, $1,856 (1,513) • Laboratory, $91 (125)	

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
				• Radiology, $92 (186) • Asthma medication, $2,713 (1,910) • Home health, $11.0 (52) *Asthma-related costs for eosinophil < 300 cells/mm^3 (n=160)* • Total, $3,383 (2,673) • Hospital, $207 (1,294) • ED, $14 (59) • Outpatient: uncontrolled asthma, $144 (186) • Outpatient: controlled asthma, $306 (307) • Asthma medication, $2,713 (1,910) Costs also reported by other eosinophil cut-off points (150 and 400 cells/mm^3) in the publication	
Zein 2016 (Zein et al. 2016) US	Payer 1 year	Patients were included if they had a principal diagnosis of asthma **Definition**	Data was abstracted from the 2011 and 2012 Nationwide Inpatient Sample (NIS)	***Mean (95% CI) annual costs*** *NIS 2011* • Hospital charges, $13,131 (3,7685-23,138)	**Mean annual (95% CI)** *NIS 2011* • Hospital length of stay (days), 2.00 (2.00-4.00)

Reference Country Currency	Perspective/ timeframe/ study design	Population and definition of severe asthma	Data source/ collection period/patient characteristics	Direct costs	Resource utilisation
$, 2011 & 2012	Prospective observational study	*Severe asthma*: patients received continuous or near continuous treatment with oral CS, or the need for high-dose ICS therapy		• Total hospital costs, $4,106 (2,565-6,621) *NIS 2012* • Hospital charges, $13,397 (7,817-23,597) • Total hospital costs, $4,099 (2,559-6,675)	*NIS 2012* Hospital length of stay (days), 2.00 (1.00-4.00)

Intervention and comparators' costs and resource use

Intervention and active comparator drug costs are shown in Table 89 and Table 90. The primary comparator in this appraisal is SoC which is associated with no additional drug costs. Drug costs for mepolizumab and reslizumab were based on the list price reported in the British National Formulary.

Table 89: Unit costs associated with the technology in the economic model

Medicine	Strength	Cost/Unit	Source
Add-on benralizumab	100mg	List: £1955/vial PAS Price: £[redacted]	AstraZeneca
Add-on mepolizumab	100mg	List: £840	(BNF 2017)
Add-on reslizumab	2.5ml (25mg)	List: £124.99	(BNF 2017)
	10ml (100mg)	List: £499.99	(BNF 2017)

Table 90: Cycle costs associated with the technology in the economic model

Medicine	Strength	Cost/Cycle	Source
Add-on benralizumab	100mg	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca
Add-on mepolizumab	100mg	£420	(BNF 2017)
Add-on reslizumab	2.5ml (25mg)	£62.50	(BNF 2017)
	10ml (100mg)	£249.99	(BNF 2017)

The unit cost of benralizumab reflects the cost per 8 weeks, and therefore will be divided by 4 to adjust to the 2-weekly cycle length. Due to the initiation phase of treatment with benralizumab, where benralizumab is injected every 4 weeks for the first 3 applications and then subsequently every 8 weeks, the first year of treatment is more expensive than the subsequent years. Therefore, patients are assumed to receive 8 doses of benralizumab in the first year and 6.5 doses thereafter, cycle costs are calculated accordingly.

The unit cost of mepolizumab reflects the cost per 4-weeks, as it is administered once every four weeks for all patients, the cost is adjusted to the 2-week cycle length.

Reslizumab is administered as an intravenous infusion every 4 weeks and the exact dosing depends on a patient's weight. It is available as a 2.5- or 10-ml vial (25mg and 100mg).

The per patient cost of reslizumab can therefore range from approximately £6,499.87 per patient per year for a patient weighing between 35-41kg, a 10-ml dose administered every 4 weeks to approximately £37,373.96 per patient per year for a patient weighing between 192-199kg, a 57.5 ml dose (the maximum recommended dose in the SmPC) administered every 4 weeks.

The estimated average annual cost per adult patient on add-on reslizumab has been calculated based on the average patient weight published in the reslizumab NICE STA TA479 of 75.2kg. This average patient would require 22.5ml of reslizumab at a cost of £1,124.97 per 4 weeks and adjusted to the 2-week cycle length accordingly.

It is known that both reslizumab and mepolizumab have patient access schemes, however, due to the confidential nature of these patient access schemes the net price of these medicines is unknown. Therefore, the analysis for the comparisons of benralizumab vs mepolizumab and reslizumab will be performed based on the list price of these medicines as per the advice received during the Decision Problem meeting for benralizumab.

Estimated average cost of SoC

SoC was derived from the key pivotal trials and defined as high dose ICS/LABA. This is costed using relative market shares (IMS) of all ICS/LABA combinations based on BNF prices 2017. A summary is provided in Table 91. Note that ICS and LABA were recorded in the trial as separates but have been costed to reflect clinical practice – use of combination ICS/LABA therapy as directed by the BTS/SIGN guidelines. High dose was defined as at least 800ug fluticasone equivalent.

Table 91: Calculation of weighted average ICS/LABA costs

ICS/LABA	Cost per inhaler	Unit	Strength	Dose/day	Cost/ Cycle	Mkt Share
Fostair	£29.32	120	200/6	4	£13.72	25.1%
Flutiform	£45.56	120	10/250	4	£21.32	5.9%
Symbicort	£28	60	400/12	4	£26.21	28.3%
Duoresp	£29.97	60	320/9	4	£28.05	7.2%
Seretide Accuhaler	£40.92	60	50/500	2	£19.15	11.4%
Seretide Evohaler	£59.48	120	25/250	4	£27.83	9.5%
Relvar	£29.50	30	22/184	1	£13.80	5.7%
AirFluSal	£39.95	120	25/250	4	£18.69	0
Sirdupla	£44.61	120	25/250	4	£20.88	7.0%
Sereflo	£39.95	120	25/250	4	£18.69	0
Weighted Average					**£21.21**	

Administration costs

It is assumed that all administrations for a biologic therapy are undertaken by a specialist asthma nurse, the relative time taken to administer has been taken from the relevant NICE STA publications, see Table 92. The time assumed in the mepolizumab STA includes reconstitution time for mepolizumab, and therefore there is an assumption that the administration of benralizumab would take less time as there is no need for reconstitution.

The cost of conducting a routine full blood count to identify the persistent eosinophil threshold for potential eligible biologic patients has not been included as this is currently conducted at routine attendances for severe asthma patients irrespective of whether they are started on a biologic. This is consistent with previous appraisals for asthma biologics.

Table 92: Administration costs applied in the economic model

Treatment	Administration time (mins)	Unit cost (per hour)	Cost per administration	Source
SoC	0	N/A	N/A	Assumption
Benralizumab	5	£108	£9	Assumption of time saving vs mepolizumab
Mepolizumab	10	£108	£18	Mepolizumab for treating severe refractory eosinophilic asthma (TA431) (NICE 2017) (PSSRU 2016)
Reslizumab	55	£108	£99	Reslizumab for treating severe eosinophilic asthma TA479 (NICE 2017) (PSSRU 2016)

Health-state unit costs and resource use

As it is the source which most closely aligns with the model structure used to analyse the cost effectiveness of benralizumab and provides UK specific estimates, the resource use by health state is calculated using estimates provided in Willson et al (Willson et al. 2014, Willson et al. 2016). Willson et al used data from the PrimoTinA-asthma® clinical trial to estimate the resources used by each health state in their model. The model by Willson et al included seven different health states, whereas the current benralizumab model has four (Section B.3.2.2). Several of these health states were found to be comparable. Consequently, the levels of resource use reported in Willson et al. were also used in the current model, with adjusted unit costs. No medication costs were considered, as the costs of rescue medications and oral corticosteroids were assumed to be negligible compared to other medical costs and due to lack of robust data. Based on the definition of the model health states, no hospitalisations were accounted for in the controlled and uncontrolled health states.

The levels of healthcare resource use for 'Controlled asthma' in the benralizumab model was calculated using a weighted average of the 'Controlled asthma' and 'Partly controlled asthma' costs from Willson et al.

Table 93: Comparison of live health state definitions in Willson et al and the current benralizumab model

Willson et al (Willson et al. 2014, Willson et al. 2016)	Benralizumab Model
Controlled Asthma: ACQ<1	Controlled asthma: Asthma: ACQ <1.5 (weight of 51%) Adequately controlled asthma identified as ACQ <1 (weight of 49%)
Partly-Controlled Asthma: 1≥ ACQ<1.5	
Uncontrolled asthma: ACQ ≥1.5	Uncontrolled asthma: ACQ ≥1.5
Non-severe exacerbation: The symptoms are outside the patient's usual range of day-to-day asthma and last for at least 2 consecutive days, and/or a decrease of PEF of ≥30.	Not Included
Severe exacerbation without hospitalisation: Non-severe exacerbation + corticosteroids (at least 3 days)	Exacerbation
Severe exacerbation with hospitalisation: Severe exacerbation + hospitalisation	

Unit costs (Table 94) were applied to the levels of healthcare resource use estimated by Willson. The mean cost of severe exacerbation was a weighted average of the cost of severe exacerbations leading and not leading to hospitalisation.

In the Willson study, the cycle length of the model was one week. A non-severe exacerbation was assumed to last one week whereas a severe exacerbation (with and without hospitalisation) lasted for 2 weeks. In order to align these health state costs with the model assumption that an exacerbation lasts for 8 weeks and is assigned during 4 different cycles the cost of an exacerbation is divided by 4 to avoid overestimating the true cost of exacerbations. Health state cycle costs are presented in Table 95: Costs by health state, and full cycle costs in Table 96: Health states and associated costs in the economic model

Table 94: Unit costs and medical resource use by health states (weekly) (Willson et al. 2016) (Willson et al. 2014, Willson et al. 2016)

Resource	Unit Cost	Health state		
		Controlled Asthma	Uncontrolled Asthma	Exacerbation
Outpatient Visits	**Cost per Visit**	**N visits per patient/week**		
Visit to GP	£36 (PSSRU)	0.035	0.14	1.31
Visit to Nurse	£11.10 (PSSRU)	0.059	0.16	0.94
Visit to Specialist	£160.32	0.0243	0.094	0.44
Home Visits	Cost per Visit	N visits per patient/week		
Visit from GP	£82.68 (PSSRU)	0.00507	0.025	0.21
Visit from Nurse	£19.70 (PSSRU)	0	0	0.0034
Lab Tests/Procedures	Cost per test/procedure	N procedures per patient/week		
Spirometry	£28.20 (Willson 2014)	0.027	0.049	0.30
Flu Vaccine	£6.32 (Willson 2014)	0.020	0.020	0
Desensitisation	£175.32 (Willson 2014)	0.00612	0.0087	0
Inpatient Resource used	Cost per episode	N events per patient/week		
Asthma exacerbation related hospitalisation	£2,692 (NHS ref Costs, weighted average of DZ15M/N/P)	0	0	0.028
A+E visit only	£137.74 (NHS Ref Costs, Weighted average of Emergency Medicine codes)	0	0	0.054

A+E visit + Hospitalisation	£2,829.74 (NHS Ref Costs)	0	0	0.03
Ambulance + hospitalisation	£2,788.25 (NHS Ref Costs, Weighted average of ambulance codes)	0	0	0.0016
Ambulance + A&E + Hospitalisation	£2,925.99 (NHS Ref costs)	0	0	0.003
Hospitalisation including ICU stay	£3,686.45 (NHS ref costs, DZ15M/N/P + XC06Z (ICU stay))	0	0	0.009

Table 95: Costs by health state

Health State	Cycle costs
Controlled Asthma	£16.38
Uncontrolled Asthma	£53.97
Exacerbation	£736.29 (divided by 4 to adjust for cycle length £184.07)

Not possible to disaggregate by severity of exacerbation

Table 96: Health states and associated costs in the economic model per cycle

Health State	Item	Treatment Arm							
		Benralizumab		SoC		Mepolizumab		Reslizumab	
		Value	Reference	Value	Reference	Value	Reference	Value	Reference
Controlled Asthma	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption	£0		£9	NICE TA431 PSSRU	£49.5	NICE TA479 PSSRU
	SoC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF
	Health State	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU
	Total	Year 1: £[redacted] Subsequent Years: £[redacted]		£37.59		£466.59		£649.57	
Uncontrolled Asthma	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption	£0		£9	NICE TA431 PSSRU	£49.5	NICE TA479 PSSRU
	SoC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF
	Health State	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU
	Total	Year 1: £[redacted] Subsequent Years: £[redacted]		£75.18		£504.18		£687.16	
Exacerbation	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption PSSRU	£0		£9	NICE TA431	£49.5	NICE TA479 PSSRU

							PSSRU		
	SoC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF
	Health State	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU
	Total	Year 1: £[redacted] Subsequent Years: £[redacted]		£205.28		£634.28		£817.26	

Long-term costs of conditions and AEs related to chronic mOCS

In addition to the utility loss, costs of conditions and AEs related to mOCS use were also incorporated into the model. Relevant costs were calculated using data from the ZONDA trial (Table 70) and the OPRI study (AstraZeneca data on file 2017) (Table 71 and Table 97).

Annual healthcare resource use costs for each category of daily mOCS dose were also determined by the OPRI, and it was assumed that the costs were specific to each condition and event (Table 97).

Table 97: Annual healthcare resource use costs by comorbidities

Daily dose of mOCS (mg)	Type 2 diabetes mellitus	Osteoporosis	Glaucoma	Cataract	Myocardial infarction	Heart failure	Cerebrovascular accident	Renal impairment	Peptic ulcer	Pneumonia
>0 – <0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5 – <2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 – <5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 – <7.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.5 – <15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OCS=oral corticosteroid

In order to estimate the cost of comorbidities due to mOCS use, the percentage of patients with chronic conditions and events in each category of daily doses of mOCS in a year was determined as follows:

- For chronic conditions (i.e. diabetes, osteoporosis, glaucoma, heart failure, renal impairment) period prevalence (for patients with 15 years of follow up) was used. By applying this data to all cycles throughout the time horizon, it is assumed that on average the prevalence of a chronic condition is constant throughout the time horizon.
- For events (i.e. cataract, myocardial infarction, cerebrovascular accident, peptic ulcer, pneumonia) annual incidence rates were used to capture the recurrent nature of these events.

The annual costs of chronic conditions and events for each dose category were applied to estimate the cost of managing all comorbidities for each category of daily doses of mOCS. To calculate the total costs of comorbidities for all mOCS patients for benralizumab and standard care groups (Table 98), the costs by mOCS exposure category were weighted by the percentage of patients in each of these categories. This was conducted for both groups at baseline and at 28 weeks.

Table 98: Cycle costs of managing comorbidities due to chronic mOCS use

Daily dose of mOCS (mg)	Benralizumab		Placebo	
	Baseline	At 28 weeks	Baseline	At 28 weeks
>0 – <0.5	[redacted]	[redacted]	[redacted]	[redacted]
0.5 – <2.5	[redacted]	[redacted]	[redacted]	[redacted]
2.5 – <5	[redacted]	[redacted]	[redacted]	[redacted]
6 – <7.5	[redacted]	[redacted]	[redacted]	[redacted]
7.5 – <15	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]
mOCS – TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

OCS=oral corticosteroid

These cost estimates were applied in the model to both benralizumab and standard care arms throughout the model's time horizon. Patients using mOCS during the initial 28 weeks incur the cost of managing comorbidities at baseline, and patients using mOCS after the 28 week period incur the cost of managing comorbidities at 28 weeks.

The impact of excluding these costs is assessed by a scenario analysis in section B.3.8 where these costs are set to zero.

Adverse reaction unit costs and resource use

AEs were not included in the model (see B.3.4).

Miscellaneous unit costs and resource use

Not applicable.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A list of all variables used in the economic analysis is provided in Table 99.

Table 99: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	SE	Distribution	Reference to section in submission

Time Horizon	Lifetime	N/A	N/A	Features of the Economic Analysis, Section B.3.2.2
Discount rates	Costs: 3.5% Outcomes: 3.5%	N/A	N/A	Features of the Economic Analysis, Section B.3.2.2
Age	50.2	0.59	Gamma	Patient Characteristics Section B.3.3.1
% female	64.5%	64.50	Beta	Patient Characteristics Section B.3.3.1
Benralizumab drug cost	£ (PAS price)	N/A	N/A	Cost and Healthcare resource use, Section B.3.5
Reslizumab drug cost	2.5ml: £124.99 (list price) 10ml: £499.99 (list price)	N/A	N/A	Cost and Healthcare resource use, Section B.3.5
Mepolizumab drug cost	£840 (list price)	N/A	N/A	Cost and Healthcare resource use, Section B.3.5
SoC	£21.21	N/A	N/A	Cost and Healthcare resource use, Section B.3.5
Administration costs	Benralizumab – £9 Mepolizumab – £18 Reslizumab – £99	Benralizumab – 0.9 Mepolizumab – 1.8 Reslizumab – 9.9	Gamma	Cost and Healthcare resource use, Section B.3.5
Health State Costs				
Controlled Asthma	£16.38	1.64	Gamma	Cost and Healthcare resource use, Section B.3.5
Uncontrolled Asthma	£53.97	5.40	Gamma	Cost and Healthcare resource use, Section B.3.5

Exacerbation	£736.29 (divided by 4 to adjust for cycle length, £184.09)	18.41	Gamma	Cost and Healthcare resource use, Section B.3.5
Health State Utility				
Controlled, non mOCS, benralizumab	0.8689	0.0179	Beta	Measurement and valuation of health effects, Section B.3.4
Controlled, non mOCS, SoC	0.8207	0.0177	Beta	Measurement and valuation of health effects, Section B.3.4
Controlled, mOCS, benralizumab	0.8478	0.0097	Beta	Measurement and valuation of health effects, Section B.3.4
Controlled, mOCS, SoC	0.8562	0.0099	Beta	Measurement and valuation of health effects, Section B.3.4
Uncontrolled, non mOCS, benralizumab	0.7325	0.0181	Beta	Measurement and valuation of health effects, Section B.3.4
Uncontrolled, non mOCS, SoC	0.7010	0.0167	Beta	Measurement and valuation of health effects, Section B.3.4
Uncontrolled, mOCS, benralizumab	0.7364	0.0165	Beta	Measurement and valuation of health effects, Section B.3.4
Uncontrolled, mOCS, SoC	0.6977	0.0137	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation non mOCS, prior HS Controlled, OCS	0.8150	0.0373	Beta	Measurement and valuation of health effects, Section B.3.4

Exacerbation non mOCS, prior HS Controlled, ER	0.8150	0.0373	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation non mOCS, prior HS Controlled, Hosp	0.6413	0.0529	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation mOCS, prior HS Controlled, OCS	0.8189	0.0264	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation mOCS, prior HS Controlled, ER	0.8189	0.0264	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation mOCS, prior HS Controlled, Hosp	0.6413	0.0529	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation non mOCS, prior HS Uncontrolled, OCS	0.7157	0.0268	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation non mOCS, prior HS Uncontrolled, ER	0.7157	0.0268	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation non mOCS, prior HS Uncontrolled, Hosp	0.6413	0.0529	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation mOCS, prior HS Uncontrolled, OCS	0.6545	0.0193	Beta	Measurement and valuation of health effects, Section B.3.4
Exacerbation mOCS, prior HS Uncontrolled, ER	0.6545	0.0193	Beta	Measurement and valuation of health effects, Section B.3.4

Exacerbation mOCS, prior HS Uncontrolled, Hosp	0.6413	0.0529	Beta	Measurement and valuation of health effects, Section B.3.4
Response Assessment				
Benralizumab response assessment (weeks)	52	0.00	Gamma	Transition Probabilities Section B.3.3.2
OCS sparing period (weeks)	28	0.00	Gamma	Transition Probabilities Section B.3.3.2
Risk of discontinuation of add-on therapy (annual)	0.118	11.8	Beta	Transition Probabilities Section B.3.3.2
Benralizumab - % of responders (mOCS)	[redacted]	-	Beta	Transition Probabilities Section B.3.3.2
Benralizumab - % of responders (non mOCS)	[redacted]	-	Beta	Transition Probabilities Section B.3.3.2
Exacerbation Distribution				
Benralizumab exacerbation distribution – mOCS, prior controlled, OCS burst	100%	0	Dirichlet	Distribution of Exacerbations Section B.3.3.3
Benralizumab exacerbation distribution – mOCS, prior controlled, A+E	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – mOCS, prior controlled, Hosp	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior controlled, OCS burst	100%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior controlled, A+E	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior controlled, Hosp	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2

Benralizumab exacerbation distribution – mOCS, prior uncontrolled, OCS burst	100%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – mOCS, prior uncontrolled, A+E	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – mOCS, prior uncontrolled, Hosp	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior uncontrolled, OCS burst	81.48%	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior uncontrolled, A+E	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
Benralizumab exacerbation distribution – non mOCS, prior uncontrolled, Hosp	18.52%	0.07	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – mOCS, prior controlled, OCS burst	100%	0	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – mOCS, prior controlled, A+E	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – mOCS, prior controlled, Hosp	0%	0	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior controlled, OCS burst	89.29%	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior controlled, A+E	3.57%	0.07	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior controlled, Hosp	7.14%	0.06	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – mOCS, prior uncontrolled, OCS burst	68.89%	0.04	Dirichlet	Transition Probabilities Section B.3.3.2

SoC exacerbation distribution – mOCS, prior uncontrolled, A+E	11.11%	0.07	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – mOCS, prior uncontrolled, Hosp	20%	0.07	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior uncontrolled, OCS burst	85.34%	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior uncontrolled, A+E	7.75%	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
SoC exacerbation distribution – non mOCS, prior uncontrolled, Hosp	6.91%	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Asthma Mortality				
Asthma mortality - OCS Burst - 17-44	0.0005	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - OCS Burst - 45-100	0.0032	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality – A+E Visit - 17-44	0.0032	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality – A+E Visit - 45-100	0.0205	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - Hospitalisation 18-24	0.0015	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - Hospitalisation 25-34	0.0014	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - Hospitalisation 35-44	0.0020	0.0000	Beta	Clinical parameters and variables Section B.3.3

Asthma mortality - Hospitalisation 45-54	0.0076	0.0000	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - Hospitalisation 55-64	0.0214	0.0010	Beta	Clinical parameters and variables Section B.3.3
Asthma mortality - Hospitalisation 65-100	0.0454	0.0010	Beta	Clinical parameters and variables Section B.3.3
Costs				
Administration costs - Benralizumab	£9.0	0.9	Gamma	Cost and Healthcare Resource Use Section B.3.5
Health state costs - Controlled	£16.38	1.64	Gamma	Cost and Healthcare Resource Use Section B.3.5
Health state costs - Uncontrolled	£53.97	5.40	Gamma	Cost and Healthcare Resource Use Section B.3.5
Health state costs - Exacerbation	£184.07	18.41	Gamma	Cost and Healthcare Resource Use Section B.3.5
mOCS Inputs				
% mOCS at baseline	54.10%	0	Gamma	Patient Characteristics Section B.3.3.1
Benralizumab - % with complete OCS sparing	30.10%	0.08	Gamma	Table 65
Standard Care - % with complete OCS sparing	10.70%	0.03	Gamma	Table 65
Period Prevalence of Type 2 Diabetes, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Type 2 Diabetes, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Type 2 Diabetes, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Type 2 Diabetes, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68

Period Prevalence of Type 2 Diabetes, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Type 2 Diabetes, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Osteoporosis, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Glaucoma, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Cataracts, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68

Period Prevalence of MI, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of MI, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of MI, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of MI, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of MI, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of MI, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Heart Failure, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Stroke, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Renal Impairment, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Renal Impairment, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68

Period Prevalence of Renal Impairment, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Renal Impairment, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Renal Impairment, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Renal Impairment, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Peptic Ulcer, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 0-0.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 0.5-2.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 2.5-5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 5-7.5mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 7.5-15mg mOCS	[redacted]	0.00	Beta	Table 68
Period Prevalence of Pneumonia, daily dose 15+mg mOCS	[redacted]	0.00	Beta	Table 68
Cost of Type 2 Diabetes, daily dose 0-0.5mg mOCS	[redacted]	12.02	Gamma	Table 94
Cost of Type 2 Diabetes, daily dose 0.5-2.5mg mOCS	[redacted]	5.98	Gamma	Table 94

Cost of Type 2 Diabetes, daily dose 2.5-5mg mOCS	[redacted]	15.20	Gamma	Table 94
Cost of Type 2 Diabetes, daily dose 5-7.5mg mOCS	[redacted]	77.34	Gamma	Table 94
Cost of Type 2 Diabetes, daily dose 7.5-15mg mOCS	[redacted]	61.54	Gamma	Table 94
Cost of Type 2 Diabetes, daily dose 15+mg mOCS	[redacted]	295.09	Gamma	Table 94
Cost of Osteoporosis, daily dose 0-0.5mg mOCS	[redacted]	4.18	Gamma	Table 94
Cost of Osteoporosis, daily dose 0.5-2.5mg mOCS	[redacted]	5.56	Gamma	Table 94
Cost of Osteoporosis, daily dose 2.5-5mg mOCS	[redacted]	26.10	Gamma	Table 94
Cost of Osteoporosis, daily dose 5-7.5mg mOCS	[redacted]	19.43	Gamma	Table 94
Cost of Osteoporosis, daily dose 7.5-15mg mOCS	[redacted]	40.89	Gamma	Table 94
Cost of Osteoporosis, daily dose 15+mg mOCS	[redacted]	780.00	Gamma	Table 94
Cost of Glaucoma, daily dose 0-0.5mg mOCS	[redacted]	3.74	Gamma	Table 94
Cost of Glaucoma, daily dose 0.5-2.5mg mOCS	[redacted]	6.16	Gamma	Table 94
Cost of Glaucoma, daily dose 2.5-5mg mOCS	[redacted]	11.51	Gamma	Table 94
Cost of Glaucoma, daily dose 5-7.5mg mOCS	[redacted]	16.73	Gamma	Table 94
Cost of Glaucoma, daily dose 7.5-15mg mOCS	[redacted]	14.30	Gamma	Table 94
Cost of Glaucoma, daily dose 15+mg mOCS	[redacted]	27.24	Gamma	Table 94
Cost of Cataracts, daily dose 0-0.5mg mOCS	[redacted]	15.64	Gamma	Table 94
Cost of Cataracts, daily dose 0.5-2.5mg mOCS	[redacted]	23.66	Gamma	Table 94
Cost of Cataracts, daily dose 2.5-5mg mOCS	[redacted]	58.67	Gamma	Table 94
Cost of Cataracts, daily dose 5-7.5mg mOCS	[redacted]	82.49	Gamma	Table 94
Cost of Cataracts daily dose 7.5-15mg mOCS	[redacted]	88.18	Gamma	Table 94
Cost of Cataracts, daily dose 15+mg mOCS	[redacted]	412.29	Gamma	Table 94
Cost of MI, daily dose 0-0.5mg mOCS	[redacted]	10.08	Gamma	Table 94

Cost of MI, daily dose 0.5-2.5mg mOCS	[redacted]	10.36	Gamma	Table 94
Cost of MI, daily dose 2.5-5mg mOCS	[redacted]	36.32	Gamma	Table 94
Cost of MI, daily dose 5-7.5mg mOCS	[redacted]	85.59	Gamma	Table 94
Cost of MI, daily dose 7.5-15mg mOCS	[redacted]	40.19	Gamma	Table 94
Cost of MI, daily dose 15+mg mOCS	[redacted]	324.26	Gamma	Table 94
Cost of Heart Failure, daily dose 0-0.5mg mOCS	[redacted]	8.58	Gamma	Table 94
Cost of Heart Failure, daily dose 0.5-2.5mg mOCS	[redacted]	12.10	Gamma	Table 94
Cost of Heart Failure, daily dose 2.5-5mg mOCS	[redacted]	25.13	Gamma	Table 94
Cost of Heart Failure, daily dose 5-7.5mg mOCS	[redacted]	41.06	Gamma	Table 94
Cost of Heart Failure, daily dose 7.5-15mg mOCS	[redacted]	42.96	Gamma	Table 94
Cost of Heart Failure, daily dose 15+mg mOCS	[redacted]	277.95	Gamma	Table 94
Cost of Stroke, daily dose 0-0.5mg mOCS	[redacted]	15.86	Gamma	Table 94
Cost of Stroke, daily dose 0.5-2.5mg mOCS	[redacted]	11.31	Gamma	Table 94
Cost of Stroke, daily dose 2.5-5mg mOCS	[redacted]	40.68	Gamma	Table 94
Cost of Stroke, daily dose 5-7.5mg mOCS	[redacted]	94.51	Gamma	Table 94
Cost of Stroke, daily dose 7.5-15mg mOCS	[redacted]	47.56	Gamma	Table 94
Cost of Stroke, daily dose 15+mg mOCS	[redacted]	419.96	Gamma	Table 94
Cost of Renal Impairment, daily dose 0-0.5mg mOCS	[redacted]	10.12	Gamma	Table 94
Cost of Renal Impairment, daily dose 0.5-2.5mg mOCS	[redacted]	8.10	Gamma	Table 94
Cost of Renal Impairment, daily dose 2.5-5mg mOCS	[redacted]	21.42	Gamma	Table 94
Cost of Renal Impairment, daily dose 5-7.5mg mOCS	[redacted]	70.65	Gamma	Table 94
Cost of Renal Impairment, daily dose 7.5-15mg mOCS	[redacted]	29.68	Gamma	Table 94
Cost of Renal Impairment, daily dose 15+mg mOCS	[redacted]	179.30	Gamma	Table 94

Cost of Peptic Ulcer, daily dose 0-0.5mg mOCS	[redacted]	3.04	Gamma	Table 94
Cost of Peptic Ulcer, daily dose 0.5-2.5mg mOCS	[redacted]	9.38	Gamma	Table 94
Cost of Peptic Ulcer, daily dose 2.5-5mg mOCS	[redacted]	8.01	Gamma	Table 94
Cost of Peptic Ulcer, daily dose 5-7.5mg mOCS	[redacted]	66.71	Gamma	Table 94
Cost of Peptic Ulcer, daily dose 7.5-15mg mOCS	[redacted]	18.81	Gamma	Table 94
Cost of Peptic Ulcer, daily dose 15+mg mOCS	[redacted]	337.37	Gamma	Table 94
Cost of Pneumonia, daily dose 0-0.5mg mOCS	[redacted]	3.47	Gamma	Table 94
Cost of Pneumonia, daily dose 0.5-2.5mg mOCS	[redacted]	5.06	Gamma	Table 94
Cost of Pneumonia, daily dose 2.5-5mg mOCS	[redacted]	23.61	Gamma	Table 94
Cost of Pneumonia, daily dose 5-7.5mg mOCS	[redacted]	59.49	Gamma	Table 94
Cost of Pneumonia, daily dose 7.5-15mg mOCS	[redacted]	55.21	Gamma	Table 94
Cost of Pneumonia, daily dose 15+mg mOCS	[redacted]	162.21	Gamma	Table 94
Disutility of Type 2 Diabetes	0.0621	0.00	Beta	Table 83
Disutility of Osteoporosis	0.0418	0.01	Beta	Table 83
Disutility of Glaucoma	0.0278	0.01	Beta	Table 83
Disutility of Cataract	0.0271	0.01	Beta	Table 83
Disutility of MI	0.0557	0.01	Beta	Table 83
Disutility of Heart Failure	0.1167	0.01	Beta	Table 83
Disutility of Stroke	0.1009	0.01	Beta	Table 83
Disutility of Renal Impairment	0.0963	0.01	Beta	Table 83
Disutility of Peptic Ulcer	0.0552	0.01	Beta	Table 83
Disutility of Pneumonia	0.0790	0.04	Beta	Table 83
Transition Probabilities				
Transition probability – mOCS C-C Pre-assessment	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-UC Pre-assessment	[redacted]	0.05	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability - mOCS C-EC Pre-assessment	[redacted]	0.05	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-EUC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – mOCS UC-UC Pre-assessment	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-C Pre-assessment	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EUC Pre-assessment	[redacted]	0.05	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EC Pre-assessment	[redacted]	0.35	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-C Pre-assessment	[redacted]	0.43	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-UC Pre-assessment	[redacted]	0.43	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EUC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-EUC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-C Pre-assessment	[redacted]	0.24	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-UC Pre-assessment	[redacted]	0.20	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability - mOCS EUC-EC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-C Responders	[redacted]	0.01	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-UC Responders	[redacted]	0.05	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-EC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-EUC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-UC Responders	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-C Responders	[redacted]	0.05	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EUC Responders	[redacted]	0.06	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EC Responders	[redacted]	0.35	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-C Responders	[redacted]	0.43	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-UC Responders	[redacted]	0.43	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EUC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability - mOCS EUC-EUC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-C Responders	[redacted]	0.43	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-UC Responders	[redacted]	0.25	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-EC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-C SoC	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-UC SoC	[redacted]	0.06	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-EC SoC	[redacted]	0.07	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS C-EUC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-UC SoC	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-C SoC	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS UC-EUC SoC	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EC SoC	[redacted]	0.17	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability - mOCS EC-C SoC	[redacted]	0.22	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-UC SoC	[redacted]	0.19	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EC-EUC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-EUC SoC	[redacted]	0.13	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-C SoC	[redacted]	0.17	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-UC SoC	[redacted]	0.11	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability - mOCS EUC-EC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Nom mOCS C-C Pre-assessment	[redacted]	0.01	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-UC Pre-assessment	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-EC Pre-assessment	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-EUC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-UC Pre-assessment	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-C Pre-assessment	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability – Non mOCS UC-EC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-EUC Pre-assessment	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EC Pre-assessment	[redacted]	0.27	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-C Pre-assessment	[redacted]	0.08	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-UC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EUC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-EUC Pre-assessment	[redacted]	0.21	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-C Pre-assessment	[redacted]	0.19	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-UC Pre-assessment	[redacted]	0.13	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-EC Pre-assessment	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-C Responders	[redacted]	0.01	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-UC Responders	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-EC Responders	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability – Non mOCS C-EUC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-UC Responders	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-C Responders	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-EC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-EUC Responders	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EC Responders	[redacted]	0.27	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-C Responders	[redacted]	0.08	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-UC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EUC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-EUC Responders	[redacted]	0.26	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-C Responders	[redacted]	0.21	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-UC Responders	[redacted]	0.18	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-EC Responders	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability – Non mOCS C-C SoC	[redacted]	0.02	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-UC SoC	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-EC SoC	[redacted]	0.04	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS C-EUC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-UC SoC	[redacted]	0.01	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-C SoC	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-EC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS UC-EUC SoC	[redacted]	0.03	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EC SoC	[redacted]	0.19	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-C SoC	[redacted]	0.08	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-UC SoC	[redacted]	0.19	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EC-EUC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-EUC SoC	[redacted]	0.09	Dirichlet	Transition Probabilities Section B.3.3.2

Transition probability – Non mOCS EUC-C SoC	[redacted]	0.10	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-UC SoC	[redacted]	0.08	Dirichlet	Transition Probabilities Section B.3.3.2
Transition probability – Non mOCS EUC-UC SoC	[redacted]	0.00	Dirichlet	Transition Probabilities Section B.3.3.2

Assumptions

The key assumptions and their justification are detailed in the following tables.

Table 100: Key model assumptions: structural and treatment effects

Assumption	Justification	Source
Data from multicountry trials is applicable to UK	Consistent with established economic models	Norman 2013
Constant exacerbation rates for SoC and biologic add-on therapy throughout time	Consistent with established economic models and previous STAs for asthma biologics	Norman 2013 NICE TA431 and 479
Exacerbations are classified into three categories defined by the resource incurred	In line with endpoints defined in the mepolizumab clinical trial programme	SIROCCO/CALIMA/ZONDA
Patients are at risk of asthma related mortality as a result of an exacerbation	Relevant data for mortality risk of hospitalised exacerbations is identified in the systematic literature search. Non-hospitalised mortality risk is estimated from the NRAD report. Consistent with previous STAs for asthma biologics	Watson 2007 NRAD NICE TA431 and 479
In UK clinical practice assessment of response to biologic therapy will be made at 52 weeks. Non-responders discontinue biologic therapy and revert to SoC	Consistent with previous STAs for asthma biologics. Aligns with SPC for benralizumab	NICE TA431 and 479 Benralizumab draft SmPC
In patients who respond to biologic therapy, the intended treatment duration is lifetime	Consistent with previous STAs for asthma biologics.	NICE TA431 and 479
The impact of adverse drug reactions is negligible.	Minimal differences in AEs between benralizumab and placebo	CALIMA/SIROCCO/ZONDA

Patients are assumed to discontinue mOCS at the rate seen in the trial and therefore avoid the potential consequences of mOCS and their associated costs and QALY decrements	Consistent with Clinical Expert advice and with previous STAs for asthma biologics.	NICE TA431 and 278
The relative treatment effect derived from the MAIC conducted in the ITT populations for benralizumab and mepolizumab is assumed to apply in the more severe subgroup in which mepolizumab is recommended	Consistent with previous STAs for asthma biologics.	NICE TA431 and 479
The discontinuation rate of patients receiving reslizumab is equal to that of patients receiving benralizumab	Consistent with previous STAs for asthma biologics.	NICE TA431 and 479

Table 101: Key model assumptions: HRQL & Costs

Assumption	Justification	Source
There is negligible l impact of asthma related mortality on all-cause mortality	Consistent with previous STAs for asthma biologics.	NICE TA431 and 479
HRQL is treatment dependent within health states	Health states are defined based on a continuous variable (ACQ score) turned into a dichotomous variable, hence it is possible to have a different ACQ between treatments yet still be categorised into the same health state. Trial data demonstrates in health state HRQoL to be treatment dependent	SIROCCO/CALIMA/ZONDA
The association between mOCS use and long-term costs and disutilities	Consistent with previous STAs for asthma biologics. Consistent with clinical opinion. Consistent with advice received from NICE Scientific Advice	OPRI RWE study
Exacerbations last for 8 weeks	As seen in the AZ analysis of utility. The utility decrement of an exacerbation lasts for between a 7 and 10-week period	Golam et al 2017
Utility for an exacerbation requiring A+E visit is the same as that of an exacerbation requiring an OCS burst	Conservative approach due to limited data availability	-
All administrations of biologics are given by a specialist nurse	Consistent with previous STAs for asthma biologics.	NICE TA431 and 479

The administration of benralizumab takes half the time of that of mepolizumab	Assumption based on the absence of the need to reconstitute benralizumab	-
Patients experience different percentages of hospitalisations/ER/OCS exacerbations between treatments	Deemed reasonable approach from Clinician feedback Consistent with approach taken in the NICS STA for Reslizumab TA479 Observations from SIROCCO/CALIMA and ZONDA	
Differential utility values for exacerbations based on previous health state	Conservative assumption due to potential overestimation of utility decrement applied to patients experiencing an exacerbation when previously controlled Observations from SIROCCO/CALIMA and ZONDA	Consistent with previous respiratory STA for roflumilast TA461
All utility values within health states are the same between biologic treatments	Consistent with previous STAs for asthma biologics. Absence of data	NICE TA431 and 479

B.3.7 Base-case results

The following Base Case results are presented:

- Benralizumab PAS price vs SoC alone in the Base Case Population
- Benralizumab PAS price vs Mepolizumab List price in the Mepolizumab NICE recommended population
- Benralizumab PAS price vs Reslizumab List price in the Reslizumab NICE recommended population

Base-case incremental cost-effectiveness analysis results

Base case pair-wise analysis for benralizumab versus SoC alone and benralizumab versus mepolizumab and reslizumab are presented below.

Table 102 shows that the cost-effectiveness of add-on benralizumab (+PAS) compared with SoC alone is £34,284/QALY gained in the Base Case Population. Benralizumab provides an additional [redacted] QALYs at an additional cost of £[redacted] in the Base Case Population.

Table 103 shows that add-on benralizumab is dominant versus add-on mepolizumab with QALY gains of [redacted] and cost savings of £[redacted] in the mepolizumab NICE recommended population. However, given that this value does not include the PAS price of mepolizumab the costs and therefore ICER would differ.

Table 104 shows that add-on benralizumab is dominant versus add-on reslizumab with QALY gains of 0 and cost savings of £[redacted] in the reslizumab NICE recommended population. However, given that this value does not include the PAS price of reslizumab the costs and therefore ICER would differ.

Table 102: Base-case results vs SoC, Base Case Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£34,284
SoC	[redacted]	[redacted]	-	-	-

Table 103: Base-case results vs Mepolizumab, Mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 104: Base-case results vs Reslizumab, Reslizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Reslizumab	[redacted]	[redacted]	-	-	-

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

The model was constructed and parameterised to enable probabilistic sensitivity analysis (PSA) to assess the uncertainty in the model inputs. Where appropriate, uncertainty has been characterised through the use of standard statistical distributions. The parameters made probabilistic are listed in Table 99.

The PSA involved undertaking 1,000 simulations, each involved a random draw from each distribution and provided an estimate of the expected costs and QALYs associated with each comparator.

Probabilistic results vs SoC (base case population)

Benralizumab accumulates total (discounted) costs of £[redacted] and [redacted] QALYs. SoC alone accumulates total (discounted) costs of £[redacted] and [redacted] QALYs. This equates to benralizumab producing an additional [redacted] QALYs at an incremental cost of £[redacted] when compared to SoC alone. This generates an ICER of £33,606.

These probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable. Table 105 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 29. Benralizumab has 0% probability of being cost effective at £20,000 per QALY gained increasing to 12% at £30,000 per QALY gained. The CEAC and CEAF are detailed in Figure 29 and Figure 30 respectively.

Table 105: Probabilistic base-case results vs SoC, Base Case population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£33,728
SoC	[redacted]	[redacted]	-	-	-

Figure 29: Incremental cost effectiveness scatter plot vs SoC, Base Case Population

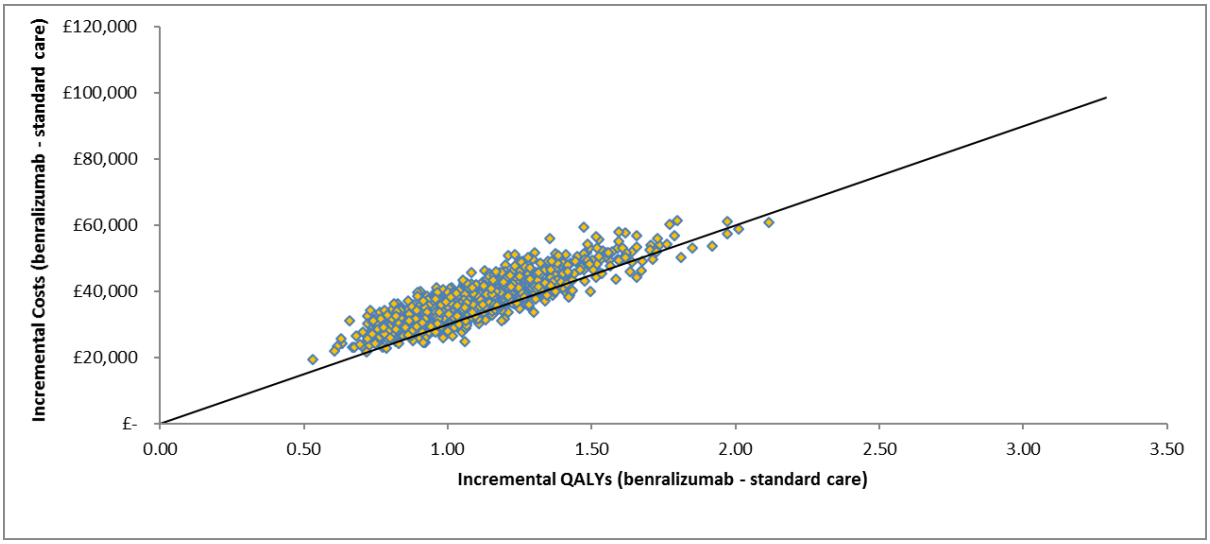
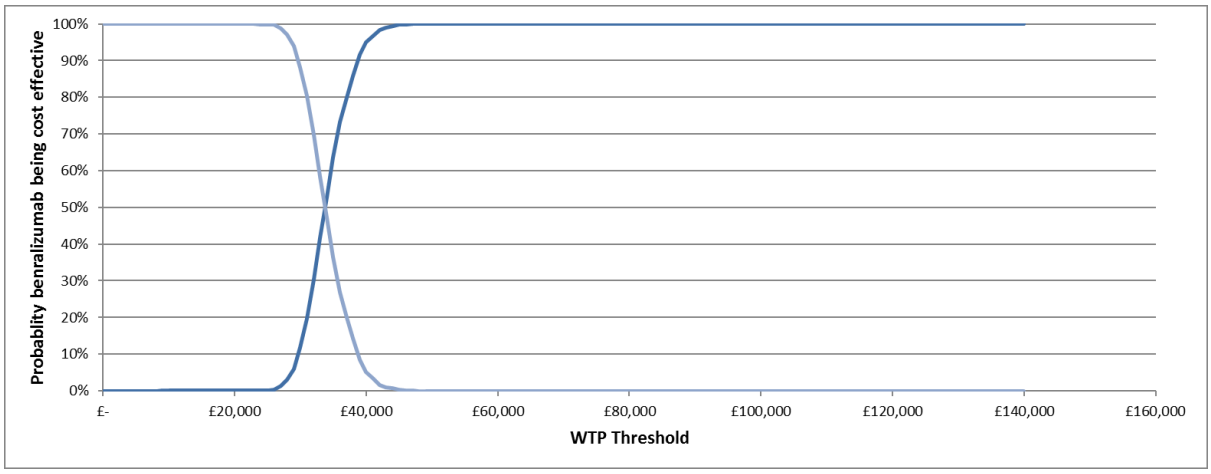


Figure 30: Cost effectiveness acceptability curve vs SoC, Base Case Population



Probabilistic results vs mepolizumab (mepolizumab NICE recommended population)

Benralizumab accumulates total (discounted) costs of £[redacted] and [redacted] QALYs. Mepolizumab accumulates total (discounted) costs of £[redacted] and [redacted] QALYs. This equates to benralizumab producing an additional [redacted] QALYs at an incremental cost of -£[redacted] when compared to mepolizumab. This results in benralizumab being dominant vs mepolizumab.

These probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable. Table 106 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 31: Incremental cost effectiveness scatter plot vs mepolizumab, mepolizumab NICE recommended population. Benralizumab has 100% probability of being cost effective at £20,000 per QALY gained and 100% at £30,000 per QALY gained. The CEAC and CEAF are detailed in Figure 31 and Figure 32 respectively.

Table 106: Probabilistic base-case results vs mepolizumab, mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Mepolizumab	[redacted]	[redacted]	-	-	-

Figure 31: Incremental cost effectiveness scatter plot vs mepolizumab, mepolizumab NICE recommended population

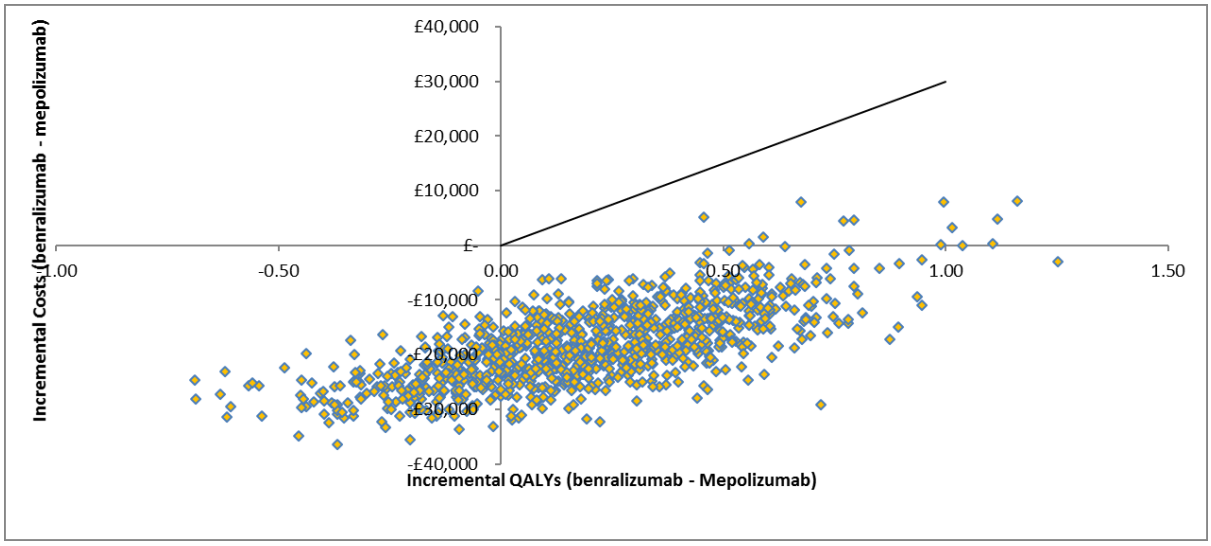
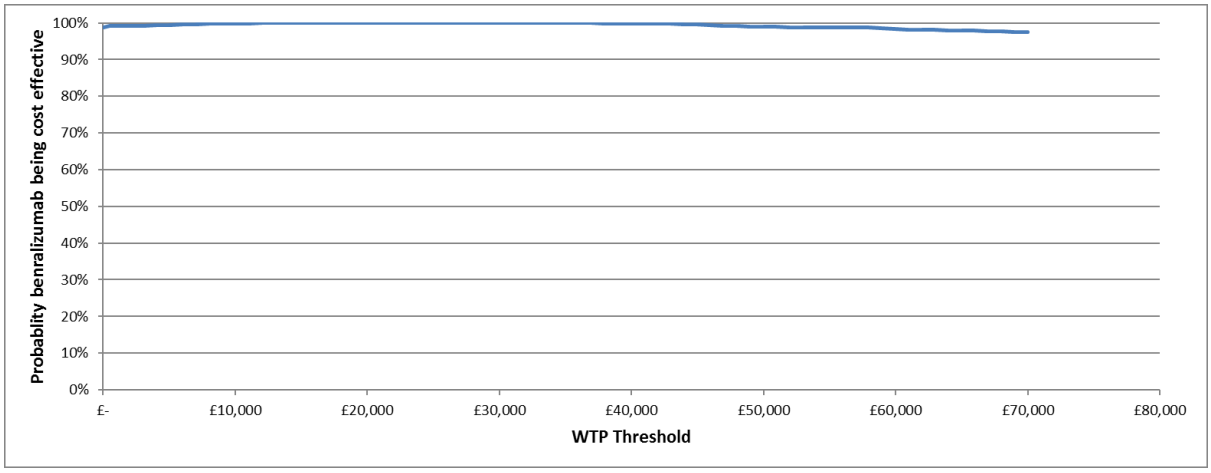


Figure 32: Cost effectiveness acceptability curve vs mepolizumab, Mepolizumab NICE reccommended population



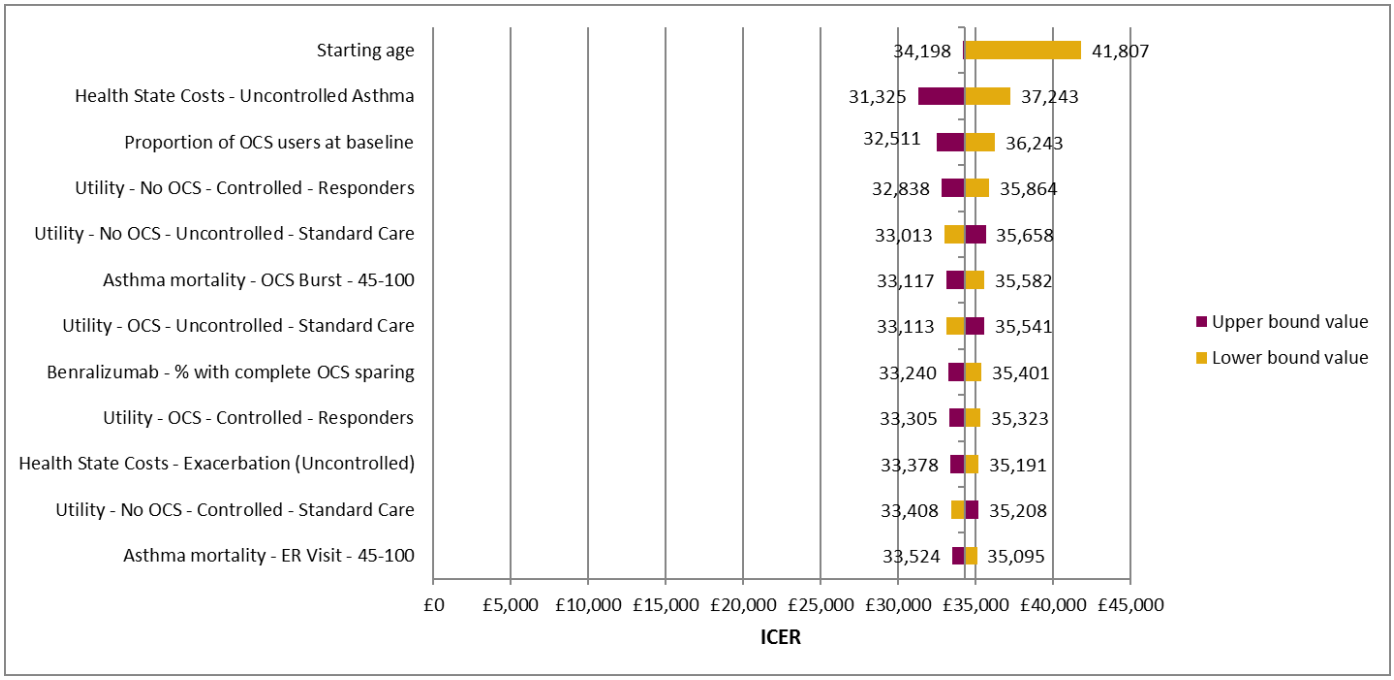
Deterministic sensitivity analysis

Vs SoC (base case population)

In order to understand the importance of each parameter in the model and the parameters' individual impact on the cost, effectiveness and cost effectiveness results, a series of deterministic sensitivity analyses were undertaken. Each parameter was set to either the upper and lower limits of the 95% CI, 20% higher or lower than the base case value (where a 95% CI was not available) or standard upper and lower limits holding all other parameters constant. Results are displayed in Figure 33 for the 12 most influential parameters on the ICER.

The most influential parameter is the Starting age of the cohort. This is due to the decrease in age related mortality at the cut off of 45 years.

Figure 33: Base-case tornado diagram, vs SoC, Base case population

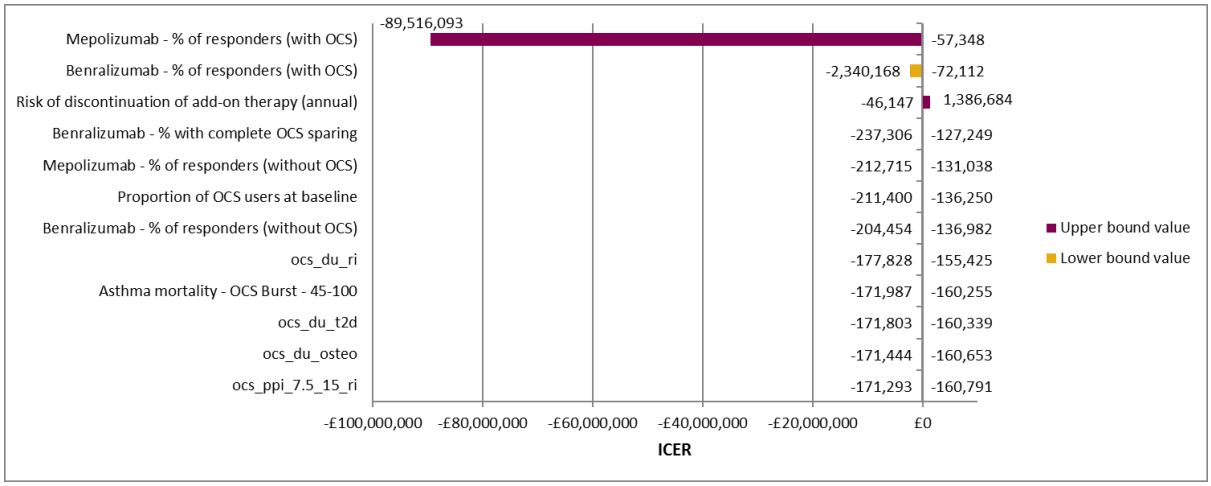


Vs mepolizumab (mepolizumab NICE recommended population)

In order to understand the importance of each parameter in the model and the parameters' individual impact on the cost, effectiveness and cost effectiveness results, a series of deterministic sensitivity analyses were undertaken. Each parameter was set to either the upper and lower limits of the 95% CI, 20% higher or lower than the base case value (where a 95% CI was not available) or standard upper and lower limits holding all other parameters constant.

The most influential parameters are the percentage of patients who respond to each treatment. This is due to the relative increase in efficacy which is seen in the responder population for each therapy.

Figure 34: Base-case tornado diagram, vs mepolizumab, mepolizumab NICE recommended population



Vs reslizumab (reslizumab NICE recommended population)

No sensitivity analyses were run vs reslizumab owing to the comparison being based on the assumption of equal efficacy, therefore any adjustment to parameters would not change the outcome.

Scenario analysis

In order to understand the importance of key assumptions within the model on the cost, effectiveness and cost effectiveness results, a number of scenario analyses were undertaken.

For all below scenarios, results are provided for the Base Case Population in the comparison vs SoC, the mepolizumab NICE reimbursed population in the comparison vs mepolizumab, and the reslizumab NICE recommended population in the comparison vs reslizumab.

- Using alternative sources for Asthma related HRQoL values.
- Utility values within states is assumed to be equal across treatment arms
- Removing the risk of Asthma death from an exacerbation
- Removing the costs associated to the consequences of mOCS
- Removing the disutilities associated to the consequences of mOCS
- Removing both the costs and disutilities associated to the consequences of mOCS
- Varying the confidential discount of Mepolizumab and Reslizumab

Using alternative sources for Asthma related HRQoL values

The base case analysis uses HRQoL values taken directly from the trial and mapped to EQ-5D-3L values as per NICEs position statement. The approach taken by the previous appraisals in this area has been to either completely rely on literature sources for utility values or to use literature sources for exacerbation disutility only.

The below scenario analyses investigate the impact of using the following sources of HRQoL:

- Willson et al and Lloyd et al for all states (Lloyd et al. 2007)
- Lloyd et al for Exacerbations only (Lloyd et al. 2007)
- EQ-5D-5L values from SIROCCO/CALIMA (note- this only affects the non mOCS patients in the model)

Willson et al and Lloyd et al for all states

This scenario follows the approach taken in the reslizumab NICE STA (TA479).

This scenario assumes that utility within each state is not treatment dependent. The states reported in the reslizumab NICE STA and the translation into this model are shown in Table 107:

Table 107: Summary of utility values from the reslizumab NICE STA

State (Reslizumab STA)	Utility Value	State (Benralizumab model)
Controlled Asthma	0.920	Controlled Asthma
Uncontrolled Asthma	0.728	Uncontrolled Asthma
Moderate Exacerbation	0.57	Exacerbation (OCS/A+E)
Severe Exacerbation	0.33	Exacerbation (Hospitalised)

Table 108: Scenario analysis; HRQoL values from Lloyd et al for all states vs SoC, Base Case population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£32,204
SoC	[redacted]	[redacted]	-	-	-

Table 109: Scenario analysis; HRQoL values from Lloyd et al for all states vs Mepolizumab, Mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 110: Scenario analysis; HRQoL values from Lloyd et al for all states vs Reslizumab, Reslizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Reslizumab	[redacted]	[redacted]	-	-	-

Lloyd et al for exacerbations

This scenario follows the approach taken in the mepolizumab NICE STA (TA431).

This scenario assumes that utility within the controlled and uncontrolled states are as per the trial while a utility decrement for an exacerbation is applied. The utility decrements reported in the mepolizumab NICE STA are shown in Table 111**:**

Table 111: Utility decrement for exacerbations

Exacerbation type	Utility Decrement	Source
Exacerbation: OCS burst	0.10	Lloyd 2007
Exacerbation: A+E	0.10	Assumption
Exacerbation: Hospitalised	0.20	Lloyd 2007

Table 112: Scenario analysis; HRQoL values from Lloyd et al for exacerbations only, vs SoC, Base Case Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)

Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£33,433
SoC	[redacted]	[redacted]	-	-	-

Table 113: Scenario analysis; HRQoL values from Lloyd et al for exacerbations only, vs mepolizumab, mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 114: Scenario analysis; HRQoL values from Lloyd et al for exacerbations only, vs reslizumab, reslizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add on Reslizumab	[redacted]	[redacted]	-	-	-

EQ-5D-5L values from SIROCCO/CALIMA

This scenario uses the EQ-5D-5L data directly from the pooled SIROCCO/CALIMA trials rather than the mapped EQ-5D-3L data in the base case. A summary of the utility values used in this scenario are given in **Error! Reference source not found.**:

Table 115: EQ-5D-5L utility values

State	Utility value: mean
Base Case Population	
Controlled, non mOCS, benralizumab	0.9188
Controlled, non mOCS, SoC	0.8797

Uncontrolled, non mOCS, benralizumab	0.8084
Uncontrolled, non mOCS, SoC	0.7840
Exacerbation, OCS (burst) prior HS Controlled, non mOCS	0.8730
Exacerbation, A+E, prior HS Controlled, non mOCS	0.8730
Exacerbation, Hospitalised prior HS Controlled, non mOCS	0.7019
Exacerbation OCS (burst), prior HS Uncontrolled, non mOCS	0.7715
Exacerbation, A+E, prior HS Uncontrolled, non mOCS	0.7715
Exacerbation, Hospitalised prior HS Uncontrolled, non mOCS	0.7019
Mepolizumab NICE recommended Population	
Controlled, non mOCS, benralizumab/mepolizumab	0.8882
Controlled, non mOCS, SoC	0.8656
Uncontrolled, non mOCS, benralizumab /mepolizumab	0.7565
Uncontrolled, non mOCS, SoC	0.7789
Exacerbation, OCS (burst) prior HS Controlled, non mOCS	0.8343
Exacerbation, A+E, prior HS Controlled, non mOCS	0.8343
Exacerbation, Hospitalised prior HS Controlled, non mOCS	0.6537
Exacerbation OCS (burst), prior HS Uncontrolled, non mOCS	0.7079

Exacerbation, A+E, prior HS Uncontrolled, non mOCS	0.7079
Exacerbation, Hospitalised prior HS Uncontrolled, non mOCS	0.6537
reslizumab NICE recommended Population	
Controlled, non mOCS, benralizumab/reslizumab	0.9191
Controlled, non mOCS, SoC	0.8744
Uncontrolled, non mOCS, benralizumab /reslizumab	0.8318
Uncontrolled, non mOCS, SoC	0.7802
Exacerbation, OCS (burst) prior HS Controlled, non mOCS	0.8875
Exacerbation, A+E, prior HS Controlled, non mOCS	0.8875
Exacerbation, Hospitalised prior HS Controlled, non mOCS	0.7624
Exacerbation OCS (burst), prior HS Uncontrolled, non mOCS	0.8158
Exacerbation, A+E, prior HS Uncontrolled, non mOCS	0.8158
Exacerbation, Hospitalised prior HS Uncontrolled, non mOCS	0.7624

Table 116: Scenario analysis; EQ-5D-5L HRQoL values from SIROCCO/CALIMA, vs SoC, Base Case Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£34,795
SoC	[redacted]	[redacted]	-	-	-

Table 117: Scenario analysis; EQ-5D-5L HRQoL values from SIROCCO/CALIMA, vs mepolizumab, mepolizumab NICE reimbursed population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 118: Scenario analysis; EQ-5D-5L HRQoL values from SIROCCO/CALIMA, vs reslizumab, reslizumab NICE reimbursed population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Reslizumab	[redacted]	[redacted]	-	-	-

Using values within states is assumed to be equal across treatment arms

The base case analysis uses treatment dependent utility values taken directly from the trial for the Controlled and Uncontrolled health states.

Table 119: EQ-5D-5L utility values

State	Utility value: mean
Base Case Population	
Controlled, non mOCS	0.8448
Controlled, mOCS	0.8520
Uncontrolled, non mOCS	0.7167
Uncontrolled, mOCS	0.7170

Mepolizumab NICE recommended Population	
Controlled, non mOCS	0.8138
Controlled, mOCS	0.8520
Uncontrolled, non mOCS	0.6861
Uncontrolled, mOCS	0.7170
Reslizumab NICE recommended Population	
Controlled, non mOCS	0.8234
Controlled, non mOCS	0.6941

The below scenario analyses investigate the impact of removing the assumption that utilities are treatment dependent.

Table 120: Scenario analysis; non-treatment dependant utility values, vs SoC, Base Case population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£38,688
SoC	[redacted]	[redacted]	-	-	-

Table 121: Scenario analysis; non-treatment dependant utility values, vs mepolizumab, mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 122: Scenario analysis; non-treatment dependant utility values, vs reslizumab, reslizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Reslizumab	[redacted]	[redacted]	-	-	-

Removing the risk of Asthma death from an exacerbation

The base case analysis assumes that there is a risk of mortality associated with an asthma exacerbation as is consistent with previous appraisals in severe asthma.

The below scenario analyses investigate the impact of removing all risk of mortality from the model.

Table 123: Scenario Analysis; Assuming no risk of mortality from an asthma exacerbation, vs SoC, Base Case Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£67,260
SoC	[redacted]	[redacted]	-	-	-

Table 124: Scenario Analysis; Assuming no risk of mortality from an asthma exacerbation, vs mepolizumab, mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 125: Scenario Analysis; Assuming no risk of mortality from an asthma exacerbation, vs reslizumab, reslizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Reslizumab	[redacted]	[redacted]	-	-	-

Removing the consequences of mOCS

The base case analysis assumes that there is a risk of a patient developing comorbidities when being treated with mOCS, and that these comorbidities have an impact on both quality of life and resource utilization.

The below scenario analyses investigate the impact of removing only the costs of these comorbidities, only the disutilities of these comorbidities and both costs and disutilities of these comorbidities.

As there are no mOCS patients in the reslizumab NICE recommended population these scenarios are not run vs reslizumab.

Table 126: Scenario Analysis; Removing the costs of mOCS comorbidities, vs SoC, Base Case Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£36,983
SoC	[redacted]	[redacted]	-	-	-

Table 127: Scenario Analysis; Removing the costs of mOCS comorbidities, vs mepolizumab, mepolizumab NICE recommended Population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 128: Scenario Analysis; Removing the disutilities of mOCS comorbidities, vs SoC, Base Case population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£37,800
SoC	[redacted]	[redacted]	-	-	-

Table 129: Scenario Analysis; Removing the disutilities of mOCS comorbidities, vs Mepolizumab, Mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Table 130: Scenario Analysis; Removing both the costs and disutilities of mOCS comorbidities, vs SoC, Base Case population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£38,573
SoC	[redacted]	[redacted]	-	-	-

Table 131: Scenario Analysis; Removing both the costs and disutilities of mOCS comorbidities, vs mepolizumab, Mepolizumab NICE recommended population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Add-on Mepolizumab	[redacted]	[redacted]	-	-	-

Varying the confidential discount of Mepolizumab and Reslizumab

It is known that both mepolizumab and reslizumab have confidential discounts, the base case analysis uses each of these comparators list prices as these are publicly available. However, in order to present results which recognises the confidential discounts available for these two comparators an analysis has been undertaken where the discount % for each of these comparators has been varied by increments of 10% between 0% and 90%.

Table 132: Scenario Analysis; Varying the mepolizumab PAS discount %, vs mepolizumab, Mepolizumab NICE recommended population

Mepolizumab PAS Discount (%)	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
0%	[redacted]	[redacted]	Benralizumab Dominant
10%	[redacted]	[redacted]	Benralizumab Dominant
20%	[redacted]	[redacted]	Benralizumab Dominant
30%	[redacted]	[redacted]	Benralizumab Dominant
40%	[redacted]	[redacted]	£19,886
50%	[redacted]	[redacted]	£66,352
60%	[redacted]	[redacted]	£112,765
70%	[redacted]	[redacted]	£159,205
80%	[redacted]	[redacted]	£205,645
90%	[redacted]	[redacted]	£252,085

Table 133: Scenario Analysis; Varying the reslizumab PAS discount %, vs reslizumab, reslizumab NICE recommended population

Reslizumab PAS Discount (%)	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
0%	[redacted]	[redacted]	Benralizumab Dominant
10%	[redacted]	[redacted]	Benralizumab Dominant
20%	[redacted]	[redacted]	Benralizumab Dominant
30%	[redacted]	[redacted]	Benralizumab Dominant
40%	[redacted]	[redacted]	Benralizumab Dominant
50%	[redacted]	[redacted]	Benralizumab Dominant
60%	[redacted]	[redacted]	Benralizumab Dominated
70%	[redacted]	[redacted]	Benralizumab Dominated
80%	[redacted]	[redacted]	Benralizumab Dominated
90%	[redacted]	[redacted]	Benralizumab Dominated

B.3.9 Subgroup analysis

No Subgroup analyses were performed

B.3.10 Validation

Validation of cost-effectiveness analysis

An advisory board with respiratory clinicians and UK health economists were undertaken to test the clinical assumptions underpinning the model and the approach to the modelling in general. During the iterative process of the economic evaluation development, the model underwent interim QCs by the model developers (COVANCE). Further the model also underwent two rounds of QC performed by an additional third party vendor (Cogentia). A QA was performed internally by an AZ analyst and covered a critique of the following:

– Completeness of model documentation and availability of the model (Excel/VBA application)

– General checklist of validity and credibility of the model

– Completeness and accuracy of reporting of model results

B.3.11 Interpretation and conclusions of economic evidence

No published studies were identified to address the NICE scope. The most relevant cost effectiveness analyses are the reslizumab and mepolizumab NICE HTA submissions; however, the level of information available (drug costs not disclosed and results reported only as ICERs by subgroup) does not allow for a comparison of the results.

Although the label for benralizumab encompasses most adult patients with severe eosinophilic asthma, the analyses presented as part of this submission focus on patients who have experienced at least three exacerbations in the year preceding treatment initiation.

Assumptions in the model surrounding mortality, the source of utilities and the length of treatment duration is as per the preferred assumptions from the previous STAs in the disease area.

Costs and outcomes were estimated based on the most relevant sources for England and the model structure and parameters were validated with clinical experts to ensure relevance to England.

The main strength of the model is that it reflects the two dimensions of asthma: symptoms and exacerbations, based on a consistent common source for benralizumab and SoC (the benralizumab SIROCCO, CALIMA and ZONDA trials).

The main limitations are summarised below:

- The matched overlap populations for benralizumab versus mepolizumab and reslizumab require an assumption that as both populations are restricted similarly the comparative treatment effect would also remain broadly comparable between both treatments.
- Given the lack of data related to exacerbations and asthma-related deaths reported in the clinical trials, it was necessary to use secondary sources of information.
- The long-term costs and consequences of mOCS use may be underestimated by the Norman et al. and OPRI data as not all chronic conditions are included.

The waning of treatment effect was not included in the model. However, given that there is no evidence to suggest that there is a loss of efficacy and that previous appraisals in this area have also not included this effect and we believe this approach is justified.

In conclusion, the results from the economic analysis show benralizumab to be a cost effective option for treating patients with severe eosinophilic asthma when compared to mepolizumab and reslizumab (using list prices), and these results do not vary significantly in several scenario and sensitivity analyses.

The results when compared to SoC show benralizumab to have an ICER slightly higher than the £30,000 threshold at £34,284 per QALY gained, this result is also stable through sensitivity and scenario analyses.

B.4 References

Accordini, S., M. Bugiani, W. Arossa, S. Gerzeli, A. Marinoni, M. Olivieri, P. Pirina, L. Carrozzi, R. Dallari, A. De Togni and R. de Marco (2006). "Poor control increases the economic cost of asthma. A multicentre population-based study." Int Arch Allergy Immunol **141**(2): 189-198.

Antonicelli, L., C. Bucca, M. Neri, B. F. De, P. Sabbatani, F. Bonifazi, H. G. Eichler, Q. Zhang and D. D. Yin (2004). "Asthma severity and medical resource utilisation." Eur. Respir. J **23**(5): 723-729.

Asthma UK (2016). "Asthma deaths in UK at highest for over a decade."

Asthma UK (2017). "Asthma facts and statistics. Available from: https://www.asthma.org.uk/about/media/facts-and-statistics/ Accessed October 2017."

AstraZeneca (2017). "Advisory board on severe asthma, London, July 2017. Summary report."

AstraZeneca (2017). Benralizumab (Fasenra) Summary of Product Characteristics.

AstraZeneca (2017). "Severe asthma advisory board. Held in London, July 2017.".

Astrazeneca data on file (2017). "Matching-adjusted indirect comparison report. Data on file."

AstraZeneca data on file (2017). "Oral corticosteroid exposure and chronic disease onset. An observational, historical cohort study to evaluate chronic disease onset associated with oral corticosteroid use and related cost impact on patients in the OPCRD/CPRD databases [manuscript in development]."

AstraZeneca data on file (2017). "Pooled subgroup analysis of the SIROCCO and CALIMA trials. Data on file."

Ayres, J. G., B. Higgins, E. R. Chilvers, G. Ayre, M. Blogg and H. Fox (2004). "Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma." Allergy **59**(7): 701-708.

Barnes, N., A. Menzies-Gow, A. H. Mansur, D. Spencer, F. Percival, A. Radwan and R. Niven (2013). "Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study." Journal of Asthma **50**(5): 529-536.

Barry, L. E., J. Sweeney, C. O'Neill, D. Price and L. G. Heaney (2017). "The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis." Respiratory Research **18**(1): 129.

Bateman, E. D., J. Bousquet, M. L. Keech, W. W. Busse, T. J. Clark and S. E. Pedersen (2007). "The correlation between asthma control and health status: the GOAL study." Eur. Respir. J **29**(1): 56-62.

Bel, E. H. W., S. E. Thompson, P. J. Prazma, C. M. Keene, O. N. Yancey, S. W. Ortega, H. G. Pavord, I. D. (2014). "Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma." N Engl J Med **371**(13): 1189-1197.

Bermejo, I., M. Stevenson, K. Cooper, S. Harnan, J. Hamilton, M. Clowes, C. Carroll, T. Harrison and S. Saha (2017). "Mepolizumab for Treating Severe Eosinophilic Asthma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal." PharmacoEconomics: 1-14.

Bime, C., C. Y. Wei, J. T. Holbrook, M. M. Sockrider, D. A. Revicki and R. A. Wise (2012). "Asthma Symptom Utility Index: Reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients." Journal of Allergy and Clinical Immunology **130**(5): 1078-1084.

Bleecker, E. R., FitzGerald, J. Mark, Chanez, Pascal, Papi, Alberto, Weinstein, Steven F. (2016). "Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial." The Lancet **388**(10056): 2115-2127.

BNF (2017). "British National Formulary. Available from: https://www.bnf.org/."

Bousquet, J., Z. Siergiejko, E. Swiebocka, M. Humbert, K. F. Rabe, N. Smith, J. Leo, C. Peckitt, R. Maykut and G. Peachey (2011). "Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma." Allergy **66**(5): 671-678.

Braunstahl, G. J., C. W. Chen, R. Maykut, P. Georgiou, G. Peachey and J. Bruce (2013). "The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma." Respir Med **107**(8): 1141-1151.

Brown, R., F. Turk, P. Dale and J. Bousquet (2007). "Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma." Allergy **62**(2): 149-153.

Brusselle, G., A. Michils, R. Louis, L. Dupont, B. Van de Maele, A. Delobbe, C. Pilette, C. S. Lee, S. Gurdain, S. Vancayzeele, P. Lecomte, C. Hermans, K. MacDonald, M. Song and I. Abraham (2009). ""Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study." Respir Med **103**(11): 1633-1642.

BTS/SIGN. (2016). "British Guideline on the Management of Asthma." 2017, from http://www.sign.ac.uk/pdf/qrg101.pdf.

Bucher, H. C., G. H. Guyatt, L. E. Griffith and S. D. Walter (1997). "The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials." J Clin Epidemiol **50**(6): 683-691.

Canadian Agency for Drugs & Technologies (2016). "Mepolizumab (Nucala). Common Drug Review Clinical Pharmacoeconomic Report."

Canadian Agency for Drugs & Technologies (2017). "Rezlizumab (Cinqair). Common Drug Review Clinical Pharmacoeconomic Report."

Carroll, A. E. and S. M. Downs (2009). "Improving decision analyses: parent preferences (utility values) for pediatric health outcomes." Journal of Pediatrics **155**(1): 21-25, 25.e21-25.

Casciano, J., J. Krishnan, Z. Dotiwala, C. Li and S. X. Sun (2017). "Clinical and Economic Burden of Elevated Blood Eosinophils in Patients With and Without Uncontrolled Asthma." J Manag Care Spec Pharm **23**(1): 85-91.

Casciano, J., J. A. Krishnan, M. B. Small, P. O. Buck, G. Gopalan, C. Li, R. Kemp and Z. Dotiwala (2016). "Burden of asthma with elevated blood eosinophil levels." BMC Pulm. Med **16**(1): 100.

Castro, M., S. Mathur, F. Hargreave, L. P. Boulet, F. Xie, J. Young, H. J. Wilkins, T. Henkel, P. Nair and G. Res-5- Study (2011). "Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study." Am J Respir Crit Care Med **184**(10): 1125-1132.

Castro, M., S. E. Wenzel, E. R. Bleecker, E. Pizzichini, P. Kuna, W. W. Busse, D. L. Gossage, C. K. Ward, Y. Wu, B. Wang, D. B. Khatry, R. van der Merwe, R. Kolbeck, N. A. Molfino and D. G. Raible (2014). "Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study." Lancet Respir Med **2**(11): 879-890.

Castro, M., J. Zangrilli, M. E. Wechsler, E. D. Bateman, G. G. Brusselle, P. Bardin, K. Murphy, J. F. Maspero, C. O'Brien and S. Korn (2015). "Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials." The Lancet Respiratory Medicine **3**(5): 355-366.

Chastek, B., S. Korrer, S. P. Nagar, F. Albers, S. Yancey, H. Ortega, M. Forshag and A. A. Dalal (2016). "Economic Burden of Illness Among Patients with Severe Asthma in a Managed Care Setting." J. Manag. Care Spec. Pharm **22**(7): 848-861.

Chauhan, A. J. (2017). "Efficacy of reslizumab in adults with severe eosinophilic asthma with ≥3 exacerbations in the previous year: analyses at weeks 16 and 52 of two placebo-controlled phase 3 trials. Abstract no. 2626. European Respiratory Society, Milan 2017. Available from: http://goo.gl/Z7dQQt."

Chen, H., M. K. Gould, P. D. Blanc, D. P. Miller, T. V. Kamath, J. H. Lee, S. D. Sullivan and T. S. Group (2007). "Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease." Journal of Allergy & Clinical Immunology **120**(2): 396-402.

Chen, H. C., C. D. Huang, E. Chang and H. P. Kuo (2016). "Efficacy of omalizumab (Xolair) in patients with moderate to severe predominately chronic oral steroid dependent asthma in Taiwan: a retrospective, population-based database cohort study." BMC Pulmonary Medicine **16**: 3.

Chen, W., L. D. Lynd, J. M. FitzGerald and M. Sadatsafavi (2016). "Influences of Socioeconomic Status on Costs of Asthma Under Universal Health Coverage." Medical Care **54**(8): 789-795.

Chiner, E., E. Fernandez-Fabrellas, P. Landete, L. Novella, M. Ramon, J. N. Sancho-Chust, C. Senent and J. Berraondo (2016). "Comparison of Costs and Clinical Outcomes Between Hospital and Outpatient Administration of Omalizumab in Patients With Severe Uncontrolled Asthma." Arch Bronconeumol **52**(4): 211-216.

Chung, K. F., S. E. Wenzel, J. L. Brozek, A. Bush, M. Castro, P. J. Sterk, I. M. Adcock, E. D. Bateman, E. H. Bel, E. R. Bleecker, L. P. Boulet, C. Brightling, P. Chanez, S. E. Dahlen, R. Djukanovic, U. Frey, M. Gaga, P. Gibson, Q. Hamid, N. N. Jajour, T. Mauad, R. L. Sorkness and W. G. Teague (2014). "International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma." Eur Respir J **43**(2): 343-373.

Chupp, G. L., E. S. Bradford, F. C. Albers, D. J. Bratton, J. Wang-Jairaj, L. M. Nelsen, J. L. Trevor, A. Magnan and A. Ten Brinke (2017). "Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial." Lancet Respir Med **5**(5): 390-400.

Clinicaltrials.gov (2017). "Study to Assess Functionality, Reliability, and Performance of a Pre-filled Syringe With Benralizumab Administered at Home. Last updated June 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02417961."

Dal Negro, R. W., L. Pradelli, S. Tognella, C. Micheletto and S. Iannazzo (2011). "Cost-utility of add-on omalizumab in difficult-to-treat allergic asthma in Italy." European Annals of Allergy & Clinical Immunology **43**(2): 45-53.

Dal Negro, R. W., S. Tognella and L. Pradelli (2012). "A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy." J Asthma **49**(8): 843-848.

Dalal, A. A., M. S. Duh, L. Gozalo, M. N. Robitaille, F. Albers, S. Yancey, H. Ortega, M. Forshag, X. Lin and P. Lefebvre (2016). "Dose-Response Relationship Between Long-Term Systemic Corticosteroid Use and Related Complications in Patients with Severe Asthma." Journal of Managed Care & Specialty Pharmacy **22**(7): 833-847.

Darba, J., G. Ramirez, J. L. Garcia-Rivero, S. Mayoralas-Alises, J. F. Pascual, A. Roger, D. Vargas and A. Bijedic (2016). "A budget impact analysis of Spiromax compared with Turbuhaler for the treatment of moderate to severe asthma: A potential improvement in the inhalation technique to strengthen medication adherence could represent savings for the Spanish Healthcare System and five Spanish regions." ClinicoEconomics and Outcomes Research **8**: 435-444.

de Groot, J. C., H. Storm, M. Amelink, S. B. de Nijs, E. Eichhorn, B. H. Reitsma, E. H. D. Bel and A. ten Brinke (2016). "Clinical profile of patients with adult-onset eosinophilic asthma." ERJ Open Research **2**(2): 00100-02015.

de Groot, J. C., A. ten Brinke and E. H. D. Bel (2015). "Management of the patient with eosinophilic asthma: a new era begins." ERJ Open Research **1**(1): 00024-02015.

Dean, B. B., B. M. Calimlim, S. L. Kindermann, R. K. Khandker and D. Tinkelman (2009). "The impact of uncontrolled asthma on absenteeism and health-related quality of life." J Asthma **46**(9): 861-866.

del Carmen Vennera, M., A. Valero, E. Uria, C. Forne and C. Picado (2016). "Cost-Effectiveness Analysis of Omalizumab for the Treatment of Severe Persistent Asthma in Real Clinical Practice in Spain." Clinical Drug Investigation **36**(7): 567-578.

Devlin, N. J., K. K. Shah, Y. Feng, B. Mulhern and B. van Hout (2017). "Valuing health-related quality of life: An EQ-5D-5L value set for England." Health Econ.

Dilokthornsakul, P., T. A. Lee, T. Dhippayom, N. Jeanpeerapong and N. Chaiyakunapruk (2016). "Comparison of Health Care Utilization and Costs for Patients with Asthma by Severity and Health Insurance in Thailand." Value in Health Regional Issues **9**: 105-111.

Edelen, M. O., M. A. Burnam, K. E. Watkins, J. J. Escarce, H. Huskamp, H. H. Goldman and G. Rachelefsky (2008). "Obtaining utility estimates of the health value of commonly prescribed treatments for asthma and depression." Medical Decision Making **28**(5): 732-750.

EMA (2016). Nucala (Mepolizumab) - Summary of Product Characteristics.

EMA (2016). Xolair (Omalizumab) - Summary of Product Characteristics.

EMA (2017). Cinqaero (Reslizumab) - Summary of Product Characteristics.

ENFUMOSA (2003). "The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma." Eur. Respir. J **22**(3): 470-477.

Fahy, J. V. (2015). "Type 2 inflammation in asthma--present in most, absent in many." Nat Rev Immunol **15**(1): 57-65.

Faria, R., C. McKenna and S. Palmer (2014). "Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis." Value in Health **17**(8): 772-782.

Ferguson, G. T., J. M. FitzGerald, E. R. Bleecker, M. Laviolette, D. Bernstein, C. LaForce, L. Mansfield, P. Barker, Y. Wu, M. Jison, M. Goldman and B. S. Investigators (2017). "Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Respir Med **5**(7): 568-576.

Ferreira, L. N., U. Brito and P. L. Ferreira (2010). "Quality of life in asthma patients." Revista Portuguesa de Pneumologia **16**(1): 23-55.

Finnell, S. M., A. E. Carroll and S. M. Downs (2012). "The utility assessment method order influences measurement of parents' risk attitude." Value Health **15**(6): 926-932.

FitzGerald, J. M., E. R. Bleecker, A. Menzies-Gow, J. G. Zangrilli, I. Hirsch, P. Metcalfe, P. Newbold and M. Goldman (2017). "Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies." Lancet Respir Med **6**(1): 51-64.

FitzGerald, J. M., E. R. Bleecker, P. Nair, S. Korn, K. Ohta, M. Lommatzsch, G. T. Ferguson, W. W. Busse, P. Barker, S. Sproule, G. Gilmartin, V. Werkstrom, M. Aurivillius and M. Goldman (2016). "Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial." Lancet **388**(10056): 2128-2141.

FitzGerald, J. M., Bleecker, Eugene R., Nair, Parameswaran, Korn, Stephanie, Ohta, Ken (2016). "Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial." The Lancet **388**(10056): 2128-2141.

Fulkerson, P. C. and M. E. Rothenberg (2013). "Targeting eosinophils in allergy, inflammation and beyond." Nat Rev Drug Discov **12**(2): 117-129.

Garcia, G., C. Taille, P. Laveneziana, A. Bourdin, P. Chanez and M. Humbert (2013). "Anti-interleukin-5 therapy in severe asthma." Eur Respir Rev **22**(129): 251-257.

Gauthier, M., A. Ray and S. E. Wenzel (2015). "Evolving Concepts of Asthma." Am J Respir Crit Care Med **192**(6): 660-668.

GEMA (2009). "Guia espanola del manejo del asma." Arch Bronconeumol **45**: 2-35.

GINA (2017). "2017 GINA Report, Global Strategy for Asthma Management and Prevention. Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ Accessed November 2017."

Golam, S. B., L.; Ouwens, M. (2017). "Exacerbation Utilities and Durations by Event Type: Estimates From Phase III Benralizumab Studies ".

Gunsoy, N., S. Cockle, L. Nelsen, F. Albers and S. Doyle (2016). "Association between EQ-5D and changes in asthma symptoms, severity, and QoI in patients with severe eosinophilic asthma." Value in Health **19 (7)**: A558.

Haldar, P., C. E. Brightling, B. Hargadon, S. Gupta, W. Monteiro, A. Sousa, R. P. Marshall, P. Bradding, R. H. Green, A. J. Wardlaw and I. D. Pavord (2009). "Mepolizumab and exacerbations of refractory eosinophilic asthma." N Engl J Med **360**(10): 973-984.

Hanania, N. A., O. Alpan, D. L. Hamilos, J. J. Condemi, I. Reyes-Rivera, J. Zhu, K. E. Rosen, M. D. Eisner, D. A. Wong and W. Busse (2011). "Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial." Ann Intern Med **154**(9): 573-582.

Heaney, L. G., C. E. Brightling, A. Menzies-Gow, M. Stevenson, R. M. Niven and N. British Thoracic Society Difficult Asthma (2010). "Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry." Thorax **65**(9): 787-794.

Hospers, J. J., J. P. Schouten, S. T. Weiss, D. S. Postma and B. Rijcken (2000). "Eosinophilia is associated with increased all-cause mortality after a follow-up of 30 years in a general population sample." Epidemiology **11**(3): 261-268.

Hyland, M. E., B. Whalley, R. C. Jones and M. Masoli (2015). "A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales." Qual Life Res **24**(3): 631-639.

Iribarren, C., I. V. Tolstykh, M. K. Miller, E. Sobel and M. D. Eisner (2012). "Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts." Am. J Epidemiol **176**(11): 1014-1024.

Ivanova, J. I., R. Bergman, H. G. Birnbaum, G. L. Colice, R. A. Silverman and K. McLaurin (2012). "Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma." J. Allergy Clin. Immunol **129**(5): 1229-1235.

Kerkhof, M., T. N. Tran, J. B. Soriano, S. Golam, D. Gibson, E. V. Hillyer and D. B. Price (2017). "Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population." Thorax: doi: 10.1136/thoraxjnl-2017-210531.

Kim, S. H., T. W. Kim, J. W. Kwon, H. R. Kang, Y. W. Lee, T. B. Kim, S. H. Kim, H. W. Park, S. W. Park, Y. S. Chang, Y. S. Cho, J. W. Park, Y. J. Cho, H. J. Yoon, S. H. Cho, B. W. Choi, H. B. Moon and K. U. Min (2012). "Economic costs for adult asthmatics according to severity and control status in Korean tertiary hospitals." J. Asthma **49**(3): 303-309.

Laviolette, M., D. L. Gossage, G. Gauvreau, R. Leigh, R. Olivenstein, R. Katial, W. W. Busse, S. Wenzel, Y. Wu, V. Datta, R. Kolbeck and N. A. Molfino (2013). "Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia." J Allergy Clin Immunol **132**(5): 1086-1096.e1085.

Lee, Y. J., S. H. Kwon, S. H. Hong, J. H. Nam, H. J. Song, J. S. Lee, E. K. Lee and J. Y. Shin (2017). "Health Care Utilization and Direct Costs in Mild, Moderate, and Severe Adult Asthma: A Descriptive Study Using the 2014 South Korean Health Insurance Database." Clinical Therapeutics **39**(3): 527-536.

Lefebvre, P., M. S. Duh, M. H. Lafeuille, L. Gozalo, U. Desai, M. N. Robitaille, F. Albers, S. Yancey, H. Ortega, M. Forshag, X. Lin and A. A. Dalal (2015). "Acute and chronic systemic corticosteroid-related complications in patients with severe asthma." J Allergy Clin Immunol **136**(6): 1488-1495.

Lefebvre, P., M. S. Duh, M. H. Lafeuille, L. Gozalo, U. Desai, M. N. Robitaille, F. Albers, S. Yancey, H. Ortega, M. Forshag, X. Lin and A. A. Dalal (2017). "Burden of systemic glucocorticoid-related complications in severe asthma." Current Medical Research & Opinion **33**(1): 57-65.

Lefebvre, P., D. Sheng and M. Lafeuille (2015). "Economic and Clinical Burden of Acute and Chronic Systemic Corticosteroid-Related Complications in Asthma Patients." Am J Respir Crit Care Med **191**: A4161.

Levy, A. N., A. R. A. J. Garcia, N. Garcia-Agua Soler and M. V. Sanjuan (2015). "Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspective." Journal of Asthma **52**(2): 205-210.

Lloyd, A., S. Doyle, S. Dewilde and F. Turk (2008). "Preferences and utilities for the symptoms of moderate to severe allergic asthma." European Journal of Health Economics **9**(3): 275-284.

Lloyd, A., D. Price and R. Brown (2007). "The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK." Primary care respiratory journal : journal of the General Practice Airways Group **16**(1): 22-27.

Manson, S. C., R. E. Brown, A. Cerulli and C. F. Vidaurre (2009). "The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use." Respiratory Medicine **103**(7): 975-994.

McTaggart-Cowan, H. M., C. A. Marra, Y. Yang, J. E. Brazier, J. A. Kopec, J. M. FitzGerald, A. H. Anis and L. D. Lynd (2008). "The validity of generic and condition-specific preference-based instruments: The ability to discriminate asthma control status." Quality of Life Research **17**(3): 453-462.

Meltzer, E. O., W. W. Busse, S. E. Wenzel, V. Belozeroff, H. H. Weng, J. Feng, Y. Chon, C. F. Chiou, D. Globe and S. L. Lin (2011). "Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation." J Allergy Clin Immunol **127**(1): 167-172.

Menzella, F., N. Facciolongo, R. Piro, D. Formisano, A. Roggeri, A. Simonazzi, C. Castagnetti, C. Carbonelli and L. Zucchi (2012). "Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up." Therapeutic Advances in Respiratory Disease **6**(2): 87-95.

Moore, W. C., E. R. Bleecker, D. Curran-Everett, S. C. Erzurum, B. T. Ameredes, L. Bacharier, W. J. Calhoun, M. Castro, K. F. Chung, M. P. Clark, R. A. Dweik, A. M. Fitzpatrick, B. Gaston, M. Hew, I. Hussain, N. N. Jarjour, E. Israel, B. D. Levy, J. R. Murphy, S. P. Peters, W. G. Teague, D. A. Meyers, W. W. Busse and S. E. Wenzel (2007). "Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program." J. Allergy Clin. Immunol **119**(2): 405-413.

Morishima, T., H. Ikai and Y. Imanaka (2013). "Cost-effectiveness analysis of omalizumab for the treatment of severe asthma in Japan and the value of responder prediction methods based on a multinational trial." Value in Health Regional Issues **2**(1): 29-36.

Mukherjee, M., R. Sehmi and P. Nair (2014). "Anti-IL5 therapy for asthma and beyond." World Allergy Organ J **7**(1): 32.

Mukherjee, M., A. Stoddart, R. P. Gupta, B. I. Nwaru, A. Farr, M. Heaven, D. Fitzsimmons, A. Bandyopadhyay, C. Aftab, C. R. Simpson, R. A. Lyons, C. Fischbacher, C. Dibben, M. D. Shields, C. J. Phillips, D. P. Strachan, G. A. Davies, B. McKinstry and A. Sheikh (2016). "The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases." BMC Med **14**(1): 113.

NAEPP (2007). "Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007." J Allergy Clin Immunol **120**(5 Suppl): S94-138.

Nair, P., M. M. Pizzichini, M. Kjarsgaard, M. D. Inman, A. Efthimiadis, E. Pizzichini, F. E. Hargreave and P. M. O'Byrne (2009). "Mepolizumab for prednisone-dependent asthma with sputum eosinophilia." N Engl J Med **360**(10): 985-993.

Nair, P., S. Wenzel, K. F. Rabe, A. Bourdin, N. L. Lugogo, P. Kuna, P. Barker, S. Sproule, S. Ponnarambil, M. Goldman and Z. T. Investigators (2017). "Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma." N Engl J Med **376**(25): 2448-2458.

National Institute for Health and Care Excellence (2013). " Omalizumab for treating severe persistent allergic asthma [TA278]."

NHS Digital (2017). "Innovation scorecard. National medicines utilisation. Available from: https://app.powerbi.com/view?r=eyJrIjoiOWMyODEwMzktYWM4ZS00ZWU2LWE1NGItNzA2NjI1ODA

yYjI5IiwidCI6IjUwZjYwNzFmLWJiZmUtNDAxYS04ODAzLTY3Mzc0OGU2MjllMiIsImMiOjh9&pageName=ReportSection1 Accessed 1/11/2017."

NHS England (2017). "Service specification number 170002/S. Specialised Respiratory Services (adult) – Severe Asthma. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf."

NICE (2013). Guide to the methods of technology appraisal.

NICE (2013). Omalizumab for treating severe persistent allergic asthma.

NICE (2017). "Asthma: diagnosis, monitoring and chronic asthma management. NICE guideline [NG80]. Available from: https://www.nice.org.uk/guidance/ng80/chapter/Recommendations#principles-of-pharmacological-treatment."

NICE (2017). Mepolizumab for treating severe refractory eosinophilic asthma. Technology appraisal guidance [TA431].

NICE (2017). "Position statement on use of the EQ-5D-5L valuation set. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf."

NICE (2017). "TA479 - Reslizumab for treating severe eosinophilic asthma. Available from: https://www.nice.org.uk/guidance/ta479."

Niven, R. M., D. Saralaya, R. Chaudhuri, M. Masoli, I. Clifton, A. H. Mansur, V. Hacking, S. McLain-Smith and A. Menzies-Gow (2016). "Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: a UK multicentre observational study (the APEX II study)." BMJ Open **6**(8): e011857.

Norman, G., R. Faria, F. Paton, A. Llewellyn, D. Fox, S. Palmer, I. Clifton, J. Paton, N. Woolacott and C. McKenna (2013). "Omalizumab for the treatment of severe persistent allergic asthma: A systematic review and economic evaluation." Health Technology Assessment **17**(52): 1-342.

Novelli, F., M. Latorre, L. Vergura, M. F. Caiaffa, G. Camiciottoli, G. Guarnieri, A. Matucci, L. Macchia, A. Vianello, A. Vultaggio, A. Celi, M. Cazzola and P. Paggiaro (2015). "Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy." Pulm Pharmacol Ther **31**: 123-129.

Nowak, R. M., J. M. Parker, R. A. Silverman, B. H. Rowe, H. Smithline, F. Khan, J. P. Fiening, K. Kim and N. A. Molfino (2015). "A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma." Am J Emerg Med **33**(1): 14-20.

NRAD (2014). Why Asthma Still Kills. The National Review of Asthma Deaths. Available from: https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths.

O'Neill, S., J. Sweeney, C. C. Patterson, A. Menzies-Gow, R. Niven, A. H. Mansur, C. Bucknall, R. Chaudhuri, N. C. Thomson, C. E. Brightling, C. O'Neill, L. G. Heaney and N. British Thoracic Society Difficult Asthma (2015). "The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry." Thorax **70**(4): 376-378.

Ojeda, P. and V. S. de Burgoa (2013). "Costs associated with workdays lost and utilization of health care resources because of asthma in daily clinical practice in Spain." Journal of Investigational Allergology and Clinical Immunology **23**(4): 234-241.

Ortega, H. G., M. C. Liu, I. D. Pavord, G. G. Brusselle, J. M. FitzGerald, A. Chetta, M. Humbert, L. E. Katz, O. N. Keene, S. W. Yancey, P. Chanez and M. Investigators (2014). "Mepolizumab treatment in patients with severe eosinophilic asthma." N Engl J Med **371**(13): 1198-1207.

Park, H. S., M. K. Kim, N. Imai, T. Nakanishi, M. Adachi, K. Ohta, Y. Tohda and G. Asian Benralizumab Study (2016). "A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan." Int Arch Allergy Immunol **169**(3): 135-145.

Pascual, R. M. and S. P. Peters (2005). "Airway remodeling contributes to the progressive loss of lung function in asthma: an overview." J Allergy Clin Immunol **116**(3): 477-486; quiz 487.

Patterson, M. F., L. Borish and J. L. Kennedy (2015). "The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma: a review." J Asthma Allergy **8**: 125-134.

Pavord, I. D., S. Korn, P. Howarth, E. R. Bleecker, R. Buhl, O. N. Keene, H. Ortega and P. Chanez (2012). "Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial." Lancet **380**(9842): 651-659.

Pavord, I. D., Korn, Stephanie Howarth, Peter Bleecker, Eugene R. Buhl, Roland Keene, Oliver N. Ortega, Hector Chanez, Pascal (2012). "Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial." The Lancet **380**(9842): 651-659.

Pavord, I. D., N. Mathieson, A. Scowcroft, R. Pedersini, G. Isherwood and D. Price (2017). "The impact of poor asthma control among asthma patients treated with inhaled corticosteroids plus long-acting beta₂-agonists in the United Kingdom: a cross-sectional analysis." NPJ Primary Care Respiratory Medicine **27**(1): 17.

Phillippo, D. M., Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ (2016). "NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE." NICE_DSU **December 2016**.

Plaza-Martin, A. M., M. C. Vennera, J. Galera and L. Herraez (2014). "Prevalence and clinical profile of difficult-to-control severe asthma in children: Results from pneumology and allergy hospital units in Spain." Allergologia et Immunopathologia **42**(6): 510-517.

Price, D., M. Fletcher and T. van der Molen (2014). "Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey." NPJ. Prim. Care Respir. Med **24**: 14009.

Price, D., A. M. Wilson, A. Chisholm, A. Rigazio, A. Burden, M. Thomas and C. King (2016). "Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice." J Asthma Allergy **9**: 1-12.

Price, D. B., A. Rigazio, J. D. Campbell, E. R. Bleecker, C. J. Corrigan, M. Thomas, S. E. Wenzel, A. M. Wilson, M. B. Small, G. Gopalan, V. L. Ashton, A. Burden, E. V. Hillyer, M. Kerkhof and I. D. Pavord (2015). "Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study." Lancet Respir Med **3**(11): 849-858.

Price, D. T., FJ; Zhi Jie, J; et al. (2017). "Oral Corticosteroids Increase Risks of Onset of Diabetes Mellitus and Osteoporosis in a UK Patient Population. Poster presented at the Chest 2017 annual meeting, Oct. 28 to Nov. 1, Toronto."

PSSRU (2016). "Unit costs of health and social care. 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/."

Qoltech (2017). "Measurement of Health-related Quality of Life & Asthma Control. Available from: https://www.qoltech.co.uk/acq.html."

Quirce, S., V. Plaza, C. Picado, M. Vennera and J. Casafont (2011). "Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain." J. Investig. Allergol. Clin. Immunol **21**(6): 466-471.

Roberts, N. J., J. D. Lewsey, M. Gillies, A. H. Briggs, V. Belozeroff, D. R. Globe, C. F. Chiou, S. L. Lin and G. Globe (2013). "Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: a retrospective cohort study from 1981 to 2009." Respir Med **107**(8): 1172-1177.

Rosenberg, H. F., K. D. Dyer and P. S. Foster (2013). "Eosinophils: changing perspectives in health and disease." Nat Rev Immunol **13**(1): 9-22.

Schleich, F. D., S.; Renaud, L. (2016). "Biomarkers in the Management of Difficult Asthma." Curr Top Med Chem. 2016 Apr; 16(14): 1561–1573.

Schleich, F. N., M. Manise, J. Sele, M. Henket, L. Seidel and R. Louis (2013). "Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation." BMC Pulm Med **13**: 11.

Scottish Medicines Consortium (2016). Mepolizumab 100mg powder for solution for injection (Nucala®). SMC No. (1149/16).

Siergiejko, Z., E. Swiebocka, N. Smith, C. Peckitt, J. Leo, G. Peachey and R. Maykut (2011). "Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients." Curr Med Res Opin **27**(11): 2223-2228.

Simpson, J. L., R. Scott, M. J. Boyle and P. G. Gibson (2006). "Inflammatory subtypes in asthma: assessment and identification using induced sputum." Respirology **11**(1): 54-61.

Smith, J. R., M. J. Noble, S. Musgrave, J. Murdoch, G. M. Price, G. R. Barton, J. Windley, R. Holland, B. D. Harrison, A. Howe, D. B. Price, I. Harvey and A. M. Wilson (2012). "The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care." Thorax **67**(12): 1052-1060.

Stahl, E., A. Lindberg, S. A. Jansson, E. Ronmark, K. Svensson, F. Andersson, C. G. Lofdahl and B. Lundback (2005). "Health-related quality of life is related to COPD disease severity." Health Qual Life Outcomes **3**: 56.

Starkie, H. J., A. H. Briggs, M. G. Chambers and P. Jones (2011). "Predicting EQ-5D values using the SGRQ." Value Health **14**(2): 354-360.

Steuten, L., S. Palmer, B. Vrijhoef, F. Van Merode, C. Spreeuwenberg and H. Severens (2007). "Cost-utility of a disease management program for patients with asthma." International Journal of Technology Assessment in Health Care **23**(2): 184-191.

Straumann, A., S. Conus, P. Grzonka, H. Kita, G. Kephart, C. Bussmann, C. Beglinger, D. A. Smith, J. Patel, M. Byrne and H. U. Simon (2010). "Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial." Gut **59**(1): 21-30.

Sullivan, P. W., J. D. Campbell, V. H. Ghushchyan and G. Globe (2015). "Outcomes before and after treatment escalation to Global Initiative for Asthma steps 4 and 5 in severe asthma." Annals of Allergy, Asthma, & Immunology **114**(6): 462-469.

Sullivan, P. W., J. D. Campbell, V. H. Ghushchyan, G. Globe, J. Lange and J. M. Woolley (2015). "Characterizing the severe asthma population in the United States: claims-based analysis of three treatment cohorts in the year prior to treatment escalation." Journal of Asthma **52**(7): 669-680.

Sullivan, P. W., J. F. Slejko, M. J. Sculpher and V. Ghushchyan (2011). "Catalogue of EQ-5D scores for the United Kingdom." Med Decis Making **31**(6): 800-804.

Sullivan, S. D., L. Rasouliyan, P. A. Russo, T. Kamath and B. E. Chipps (2007). "Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma." Allergy **62**(2): 126-133.

Suruki, R. Y., J. B. Daugherty, N. Boudiaf and F. C. Albers (2017). "The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA." BMC Pulm Med **17**(1): 74.

Suzuki, C., N. Lopes da Silva, P. Kumar, P. Pathak and S. H. Ong (2017). "Cost-effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting." Journal of Medical Economics **20**(8): 832-839.

Szende, A., N. K. Leidy, E. Stahl and K. Svensson (2009). "Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D." Qual Life Res **18**(2): 267-272.

Szende, A., K. Svensson, E. Stahl, A. Meszaros and G. Y. Berta (2004). "Psychometric and utility-based measures of health status of asthmatic patients with different disease control level." Pharmacoeconomics **22**(8): 537-547.

Talini, D., F. Novelli, E. Bacci, M. Bartoli, S. Cianchetti, F. Costa, F. L. Dente, A. Di Franco, M. Latorre, L. Malagrino, B. Vagaggini, A. Celi and P. Paggiaro (2015). "Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study." BMJ Open **5**(1): e005748.

Thomson, N. C., R. Chaudhuri, L. G. Heaney, C. Bucknall, R. M. Niven, C. E. Brightling, A. N. Menzies-Gow, A. H. Mansur and C. McSharry (2013). "Clinical outcomes and inflammatory biomarkers in current smokers and exsmokers with severe asthma." J Allergy Clin Immunol **131**(4): 1008-1016.

Tsuchiya, A., J. Brazier, E. McColl and D. Parkin (2002). "Deriving preference-based single indices from non-preference based condition-specific instruments: converting AQLQ into EQ5D indices." The University of Sheffield.

Van, G. E., L. Antonicelli, Q. Zhang, L. Laforest, D. D. Yin, G. Nocea and K. Sazonov, V (2006). "Asthma-related resource use and cost by GINA classification of severity in three European countries." Respir. Med **100**(1): 140-147.

van Nooten, F., S. Stern, G. J. Braunstahl, C. Thompson, M. Groot and R. E. Brown (2013). "Cost-effectiveness of omalizumab for uncontrolled allergic asthma in the Netherlands." J Med Econ **16**(3): 342-348.

Veroniki, A. A., S. E. Straus, C. Soobiah, M. J. Elliott and A. C. Tricco (2016). "A scoping review of indirect comparison methods and applications using individual patient data." BMC Med Res Methodol **16**: 47.

Walsh, L. J., C. A. Wong, J. Oborne, S. Cooper, S. A. Lewis, M. Pringle, R. Hubbard and A. E. Tattersfield (2001). "Adverse effects of oral corticosteroids in relation to dose in patients with lung disease." Thorax **56**(4): 279-284.

Watson, L., F. Turk, P. James and S. T. Holgate (2007). "Factors associated with mortality after an asthma admission: a national United Kingdom database analysis." Respir Med **101**(8): 1659-1664.

Wenzel, S. E. (2012). "Asthma phenotypes: the evolution from clinical to molecular approaches." Nat Med **18**(5): 716-725.

Whittington, M. D., R. B. McQueen, D. A. Ollendorf, J. A. Tice, R. H. Chapman, S. D. Pearson and J. D. Campbell (2017). "Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis." Annals of Allergy, Asthma, & Immunology **118**(2): 220-225.

Willson, J., E. D. Bateman, I. Pavord, A. Lloyd, T. Krivasi and D. Esser (2014). "Cost Effectiveness of Tiotropium in Patients with Asthma Poorly Controlled on Inhaled Glucocorticosteroids and Long-Acting Beta-Agonists." Applied Health Economics and Health Policy **12**(4): 447-459.

Willson, J., C. W. Mukuria, A. Labeit, N. Gunsoy, H. Starkie Camejo, R. Alfonso-Cristancho and J. Brazier (2016). "Development of a mapping algorithm between the SGRQ and EQ-5D-5l utility values in a severe asthma population." Value in Health **19 (7)**: A385.

Xu, X., S. O'Quinn, I. Hirsch and G. Gopalan (2017). Asthma Symptom Improvements with Benralizumab Are Associated With Improvements in Activity Functions and Quality of Life for Patients With Severe, Uncontrolled Asthma: Results of Pooled Phase III Benralizumab Studies. American Thoracic Society Annual Conference, Washington DC.

Xu, X., S. O'Quinn, I. Hirsch and G. Gopalan (2017). Impact of Asthma Control Status on Lung Function and Patient Well-being Assessments in Patients With Severe Asthma. American Thoracic Society Annual Conference, Washington DC.

Yancey, S. (2017). "Mepolizumab in patients =3 exacerbations and eosinophil count =300 cells/µL. Abstract no. 3952. European Respiratory Society, Milan 2017. Available from: goo.gl/X3eJWU

".

Zafari, Z., M. Sadatsafavi, C. A. Marra, W. Chen and J. M. FitzGerald (2016). "Cost-Effectiveness of Bronchial Thermoplasty, Omalizumab, and Standard Therapy for Moderate-to-Severe Allergic Asthma." PLoS ONE [Electronic Resource] **11**(1): e0146003.

Zeiger, R. S., M. Schatz, A. A. Dalal, W. Chen, E. Sadikova, R. Y. Suruki, A. A. Kawatkar and L. Qian (2017). "Blood Eosinophil Count and Outcomes in Severe Uncontrolled Asthma: A Prospective Study." The Journal of Allergy & Clinical Immunology in Practice **5**(1): 144-153.e148.

Zeiger, R. S., M. Schatz, A. A. Dalal, L. Qian, W. Chen, E. W. Ngor, R. Y. Suruki and A. A. Kawatkar (2016). "Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting." J Allergy Clin Immunol Pract **4**(1): 120-129.e123.

Zeiger, R. S., M. Schatz, Q. Li, W. Chen, D. B. Khatry and T. N. Tran (2017). "Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma." J Allergy Clin Immunol Pract **5**(4): 1050-1060 e1059.

Zeiger, R. S., T. N. Tran, M. Schatz, Q. Li, W. Chen, D. B. Khatry, J. Davis and A. A. Kawatkar (2017). "Drivers of health care costs for adults with persistent asthma." The Journal of Allergy & Clinical Immunology in Practice **11**: 11.

Zein, J. G., B. L. Udeh, W. G. Teague, S. M. Koroukian, N. K. Schlitz, E. R. Bleecker, W. B. Busse, W. J. Calhoun, M. Castro, S. A. Comhair, A. M. Fitzpatrick, E. Israel, S. E. Wenzel, F. Holguin, B. M. Gaston and S. C. Erzurum (2016). "Impact of Age and Sex on Outcomes and Hospital Cost of Acute Asthma in the United States, 2011-2012." PLoS ONE **11 (6)**(e0157301).

Zhang, J. Y. and S. E. Wenzel (2007). "Tissue and BAL based biomarkers in asthma." Immunol Allergy Clin North Am **27**(4): 623-632; vi.

ZONDA CSR (2016). "A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)." Clinical Study Report.

B.5 Appendices

Appendices are provided in a separate file, as requested. Please note that page numbers continue from page 312 (the last page in Document B, main submission) in the appendix file (i.e., the first page of the appendix file is numbered page 312 rather than page 1), to preserve consistency of cross-linking and accuracy of the table of contents between the two files. References cited in the appendix file are included in the full list of references in the main submission.

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Single technology appraisal

Benralizumab for treating severe eosinophilic asthma [ID1129]

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The Evidence Review Group, PenTAG, and the technical team at NICE have looked at the submission received on 11 January 2018 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **19th February 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted], Project Manager [redacted]

Yours sincerely

Eleanor Donegan
Technical Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Literature searching

1. Appendix F page 442. Please can you clarify why no separate searches for adverse event literature (without the RCT filter) were undertaken?

2. P.62. Please explain why you have not used the tested RCT filter from SIGN but have instead chosen to adapt it so that it is no longer validated?

3. Appendix D page318-322; Appendix G page 442-445. Please explain why you have not included the proprietary drug name 'Fasenra' in your search strategy?

Section A: Clarification on effectiveness data

A1. Please provide any available data on risk of relapse following discontinuation with benralizumab?

A2. CALIMA trial clinical study report (CSR), section 8.3.4.2 page 217 states that "a theoretical risk of depleting eosinophils is interference with expulsion of helminthic parasites. Patients at high risk for these infections were monitored for such infections as per local medical practice while on benralizumab". Please can you provide a definition of "patients at high risk "?

A3. ZONDA CSR, section 8.6, page 194 states "there were decreases from baseline in neutrophils and lymphocytes in the benralizumab 30 mg Q4W and Q8W groups, smaller decreases from baseline were observed in the placebo. However, the mean absolute values remained within their respective reference ranges at all post-baseline time points and there were no apparent clinical manifestations associated with these transient changes). Please can you provide a definition for "transient changes" in this context?

A4. CALIMA CSR page 297. Please provide all tables (e.g. table 12.3.2.4.1.1) and figures missing from the following sections of the CSR provided by the company to the ERG :

- 12.1Summary tables and figures, listings and narratives for demographic, baseline, concomitant medication and other patient-specific characteristics
- 12.2. Efficacy evaluation data
- 12.3 Safety evaluation data
- 12.6 Figures for efficacy, safety, and immunogenicity

A5. SIROCCO CSR page 294.Please provide all tables and figures missing from the following sections of the CSR report provided by the company to the ERG :

- 12.1.Summary tables and figures, listings and narratives f Demographic, baseline, concomitant medication and other patient-specific characteristics

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- 12.2. Efficacy evaluation data
- 12.3 Safety evaluation data
- 12.6 Figures for efficacy, safety, and immunogenicity

A6. ZONDA CSR page 205. Please provide all tables and figures missing from the following sections of the CSR report provided by the company to the ERG :

- 11.1.Summary tables and figures, listings and narratives for demographic, baseline, concomitant medication and other patient-specific characteristics
- 11.2. Efficacy evaluation data
- 11.3 Safety evaluation data
- 11.6 Figures for efficacy, safety, and immunogenicity

A7. Company submission, table 11, page 67. Please confirm whether pooled and MAIC analyses included adults solely as per the NICE scope, or whether adolescents were also included in these analyses (since they are included in some pivotal trials).

A8. Company submission. Please provide further justification for your assumptions that clinical data inputs for benralizumab and reslizumab should be the same (section B.3.3, page 163) and that the relative efficacy of benralizumab and mepolizumab can be assumed to be equal for the more severe sub-group as in the wider trial population (section B.3.3.2.2, page172), in light of differences in their mechanism of action.

A9. Company submission. Please provide further justification for why the differences in trial baseline characteristics for benralizumab and mepolizumab, which the submission acknowledges as 'key differences' (section B.3.3, page162), are not considered sufficient to render MAIC analysis unsuitable (pages.162-163), whereas the differences in baseline characteristics between benralizumab and reslizumab are considered sufficient to render MAIC analysis unsuitable (page163).

A10. Company submission, table 51 page 173. Please explain why the odds ratio (OR) is used for 'Patients with complete reduction in mOCS dose' instead of a rate ratio or risk ratio, which would be comparable with the other endpoints.

A11. Company submission, table 50 and 51 page 172-173. Please comment on the negative values for the lower confidence interval of the rate ratio for 'FEV1' (Table 50, page 172) and 'Reduction in Mocs dose' (Table 51, page173), as our understanding is that negative values for rate ratios are illogical.

A12. Economic model: Please clarify why change in rescue medication was not used as a clinical input to the model for benralizumab (model file).

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Section B: Clarification on cost-effectiveness data

B1. Company submission, section B.3.3. **,** page 162. “Exacerbation rates, quality of life and transition probabilities based on ACQ score) were derived from three benralizumab trials, a pooled analysis of CALIMA and SIROCCO for patients not on mOCS (published and unpublished data) and ZONDA for patients who are on mOCS.” Please provide individual patient level (IPD) data used in the analysis, and your analysis.

B2. Company submission, section B.3.4. , page 205. “These values were applied by combining data from the ZONDA trial, data provided by the Observational & Pragmatic Research Institute (OPRI) and condition-specific disutility values from Sullivan et al”. Please provide all the data on health-related quality-of-life, and your analysis.

B3. Company submission, section B.3.3.2. , page 166**.** “Durations across the three exacerbation event types were based on a visual inspection of mean utilities per week. Durations encompassed the week during which the mean utility starts to decline through the week during which the mean utility returns to a stable level.” Please clarify how this inspection method was applied, i.e., how ‘stable level’ was defined.

Section C: Textual clarifications and additional points

C1. Please correct “reference source not found” errors in the submission.

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If you have any queries on the technical issues raised in this letter, please contact Sana Khan, Technical Lead (Sana.Khan@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Eleanor Donegan
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Thank you for the opportunity to respond. Please note that AstraZeneca are happy to answer any further queries the ERG may have, if needed.

Literature searching

1. Appendix F page 442. Please can you clarify why no separate searches for adverse event literature (without the RCT filter) were undertaken?

   As benralizumab was not licensed in any countries when the searches were conducted, no additional non-RCT or observational studies reporting adverse events with benralizumab were expected to have been carried out, as all benralizumab studies reporting adverse events were anticipated to be captured under the RCT filter.

2. P.62. Please explain why you have not used the tested RCT filter from SIGN but have instead chosen to adapt it so that it is no longer validated?

   The existing SIGN filter was adapted to include additional search terms. All the keywords used in SIGN RCT filter are part of the current search strategy. A comparative assessment of keywords used across the submission search strategy and SIGN filter is provided below.

Submission	SIGN
'prospective study'/exp	**'Prospective Study'/exp**
'randomization'/de	**RANDOMIZATION/**
'randomisation'	
'randomization'	
random*	
randomi*	
'single blind procedure'/de	**Single Blind Procedure/**
'double blind procedure'/de	**Double Blind Procedure/**
'crossover procedure'/de	**Crossover Procedure/**
'placebo'/de	**PLACEBO/**
'clinical trial'	**Clinical Trial/**
'clinical trials'	
'controlled clinical trial'	**Controlled clinical trial/**
'controlled clinical trials'	
'controlled study'/de	
'randomised controlled trial'	**Randomized Controlled Trial/ randomi?ed controlled trial$.tw.**
'randomized controlled trial'	
'randomised controlled trials'	
'randomized controlled trials'	
rct	**rct:tw**
allocated NEAR/2 random	**(random$ adj2 allocat$):tw**
assign* NEAR/2 random*	
'random allocation'	
'random assignment'	
'randomly allocated'	
'randomly assigned'	

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Submission	SIGN
'allocated randomly'	
'assigned randomly'	
(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	**((treble or triple) adj blind$).ab,ti single blind$.ab,ti double blind$:ab,ti**
placebo*	**placebo$.tw.**
'prospective study'/de	
'clinical trial'/exp	**Phase 3 clinical trial/ Phase 4 clinical trial/**
('letter'/de OR 'abstract report'/de OR 'case report' OR 'case study'/de)	**abstract report/ or letter/ Case Study/ case report.tw.**
([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)	**Conference proceeding.pt. Conference abstract.pt. Editorial.pt. Letter.pt. Note.pt.**
'controlled clinical trial'/exp 'intervention study'/exp (clinical NEXT/1 trial*):ab,ti 'major clinical study'/exp compar*:ab,ti OR group*:ab,ti 'clinical article'/exp	

3. Appendix D page318-322; Appendix G page 442-445. Please explain why you have not included the proprietary drug name 'Fasenra' in your search strategy?

The branded name Fasenra was only made public in November 2017, at the time of US regulatory approval, and after the searches were carried out. In addition, Fasenra is not yet indexed in the electronic databases, and there are no publically available studies with Fasenra. A targeted search of Embase resulted in identification of one record, which is not relevant to the review:

Kaufman MB. Pharmaceutical approval update P and T 2018. 43:1 (22-60)

Section A: Clarification on effectiveness data

A1. Please provide any available data on risk of relapse following discontinuation with benralizumab?

No formal studies have been conducted to assess withdrawal or rebound effects. Data from a phase IIb study (shown below) indicates that blood eosinophils return to near baseline levels within about 6 months from the last dose.

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[redacted]

The two primary registration studies for benralizumab – SIROCCO & CALIMA – were approximately one year in duration. The third key study, ZONDA was a 6-month study. Patients in all three studies could be rolled over to continue open label treatment with benralizumab in a longer-term safety extension study called BORA, the results of which are not yet available. Therefore, there are currently no additional data outside of those provided for the Phase 3 studies, within the adverse events section, on risk of relapse following discontinuation with benralizumab.
Benralizumab received a first marketing authorisation for use in any country in November 2017; to date there has been very little opportunity for real world use of the product with which to generate additional safety and efficacy data of this nature.

Data from phase IIb study regarding return of eosinophilia after treatment discontinuation:

With regards to the return of eosinophilia post discontinuation of benralizumab, data from a Phase IIb, randomized, placebo-controlled, double-blind, multicentre, dose-ranging study assessed the efficacy and safety of benralizumab in adult patients (18-75 years) with uncontrolled asthma who were using medium- to high-dose inhaled corticosteroids and long-acting $beta_2$-agonists and who had experienced 2 to 6 exacerbations in the previous year[1] indicates that blood eosinophils return to near baseline levels within about 6 months from the last dose:

- Patients were randomized to receive placebo, benralizumab 2 mg, benralizumab 20 mg, or benralizumab 100 mg administered subcutaneously every 4 weeks for the first 3 doses, then every 8 weeks, up to Week 40.
- All dose levels decreased blood eosinophil counts after the first dose in patients with blood eosinophil counts ≥300 cells/μL at baseline.[2] For benralizumab 20 mg (the dose closest to the 30-mg dose selected for the Phase III studies), following the last dose at Week 40, increases in blood eosinophil counts were observed at Week 52; by Week 66 blood eosinophil counts had recovered to near baseline levels.[1,2]
- In patients with blood eosinophil counts ≥300 cells/μL at baseline, peripheral blood eosinophil recovery to ≥50 cells/μL or ≥20% of baseline value was observed at Week 66 in 94.8% of patients in the benralizumab 20 mg group (n=58).[3]

References

1. Castro M, Wenzel SE, Bleecker ER et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2:879-890.
2. Castro M, Wenzel SE, Bleecker ER et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study [supplementary appendix]. Lancet Respir Med. 2014;2:879-890.

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3. In House Data, AstraZeneca Pharmaceuticals LP. Efficacy Evaluation Data MI-CP220, Section 14.2.

A2. CALIMA trial clinical study report (CSR), section 8.3.4.2 page 217 states that "a theoretical risk of depleting eosinophils is interference with expulsion of helminthic parasites. Patients at high risk for these infections were monitored for such infections as per local medical practice while on benralizumab". Please can you provide a definition of "patients at high risk "?

The importance of eosinophils in the control of helminth infections in humans is uncertain. To mitigate the potential risk of helminth infections, subjects with an untreated helminthic parasitic infection were excluded from participation in the trials, and subjects in the studies were monitored through standard AE/SAE monitoring. There was no per protocol definition of 'patients at high risk' provided. The Investigator determined if it was appropriate to include the subjects in the trial and monitor the subjects based on local medical practice and their clinical judgement. Patients in endemic regions or having visited endemic regions or patients who are severely malnourished or immunosuppressed could potentially be considered as having a higher risk, but ultimately, physicians will have to use to their judgment and knowledge of the country/region where benralizumab will be used.

The global asthma program was executed in several countries where parasitic infections are common. No adverse events of helminth parasitic infections were reported.

A3. ZONDA CSR, section 8.6, page 194 states "there were decreases from baseline in neutrophils and lymphocytes in the benralizumab 30 mg Q4W and Q8W groups, smaller decreases from baseline were observed in the placebo. However, the mean absolute values remained within their respective reference ranges at all post-baseline time points and there were no apparent clinical manifestations associated with these transient changes). Please can you provide a definition for "transient changes" in this context?

There was no specific definition of 'transient changes' with respect to neutrophils or lymphocytes: the terminology was purely descriptive. Hematology results based on CTCAE grades were evaluated. There were few shifts of ≥2 CTCAE grades in white blood cells and the incidence of shifts from baseline was similar across treatment groups. There was no apparent association with adverse or serious adverse events related to infections. AstraZeneca considers these changes to be consistent with benralizumab's mechanism of action.

A4. CALIMA CSR page 297. Please provide all tables (e.g. table 12.3.2.4.1.1) and figures missing from the following sections of the CSR provided by the company to the ERG :

- 12.1Summary tables and figures, listings and narratives for demographic, baseline, concomitant medication and other patient-specific characteristics

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- 12.2. Efficacy evaluation data
- 12.3 Safety evaluation data
- 12.6 Figures for efficacy, safety, and immunogenicity

Following further correspondence, we have provided the requested specific tables from the CSR appendix: Tables 12.3.4.5; 12.3.5.1; 12.3.5.2. These have been attached separately and marked as commercial in confidence.

A5. SIROCCO CSR page 294. Please provide all tables and figures missing from the following sections of the CSR report provided by the company to the ERG :

- 12.1. Summary tables and figures, listings and narratives f Demographic, baseline, concomitant medication and other patient-specific characteristics
- 12.2. Efficacy evaluation data
- 12.3 Safety evaluation data
- 12.6 Figures for efficacy, safety, and immunogenicity

Following further correspondence, we have provided the requested specific tables from the CSR appendix:12.3.2.6.2; 12.3.4.3; and 12.3.5.2. These have been attached separately and marked as commercial in confidence.

A6. ZONDA CSR page 205. Please provide all tables and figures missing from the following sections of the CSR report provided by the company to the ERG :

- 11.1.Summary tables and figures, listings and narratives for demographic, baseline, concomitant medication and other patient-specific characteristics
- 11.2. Efficacy evaluation data
- 11.3 Safety evaluation data
- 11.6 Figures for efficacy, safety, and immunogenicity

Following further correspondence, we have provided the requested specific tables from the CSR appendix: Table 11.3.4.4.2; 11.3.5.1; 11.3.5.2. These have been attached separately and marked as commercial in confidence.

In relation to the data in the tables provided for all three responses above, please note that adverse events that led to treatment discontinuation were slightly more frequent in the benralizumab Q8W and Q4W groups (2%) than in the placebo groups (<1%) in

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both the SIROCCO and CALIMA studies; these events mostly involved single patients and were distributed across multiple system organ classes without an apparent pattern. Adverse events that led to treatment discontinuation in the ZONDA study were generally balanced between the benralizumab and placebo groups and without apparent pattern.

A7. Company submission, table 11, page 67. Please confirm whether pooled and MAIC analyses included adults solely as per the NICE scope, or whether adolescents were also included in these analyses (since they are included in some pivotal trials).

The adolescent patients across both benralizumab and mepolizumab trials comprised <5% of the trial population (MEPO: MENSA-4%, DREAM: <1% (1 patient); BENRA: SIROCCO: 4.4%, CALIMA: 2.3% in high dose group). As the included studies enrolled a very small number of adolescent patients, these studies were considered as representative of adult patients only. The MAIC analysis included the overall population. A sensitivity analysis was conducted to assess the impact of removing adolescent patients. There were no differences in the results after removing adolescent patients (results available on request).

A8. Company submission. Please provide further justification for your assumptions that clinical data inputs for benralizumab and reslizumab should be the same (section B.3.3, page 163) and that the relative efficacy of benralizumab and mepolizumab can be assumed to be equal for the more severe sub-group as in the wider trial population (section B.3.3.2.2, page172), in light of differences in their mechanism of action.

In the absence of head-to-head data or a feasible indirect comparison versus reslizumab, we compared baseline characteristics and ITT results between the benralizumab and reslizumab studies. Patients in the reslizumab studies had lower baseline exacerbation rates, but higher baseline eosinophil levels than in the benralizumab studies (see Tables 173, 174, and 175 in the appendix). Other key differences included the use of ACQ measures; benralizumab trials reported ACQ-6, while reslizumab trials reported ACQ-7.

The annual rate ratio for clinical asthma exacerbation reductions was 0.50 (0.37-0.67) in Study 1 and 0.41 (0.28-0.59) in Study 2 for reslizumab versus placebo. This is comparable to the exacerbation reductions rate ratio for SIROCCO of 0.49 (95% CI: 0.37 - 0.64). The rate ratio for CALIMA was less favourable than SIROCCO (RR: 0.72; 95% CI: 0.54 - 0.95); however, this can be explained by regional differences in exacerbation rates at baseline, a strong placebo response, and background medication (see page 99 of the main submission).

In terms of mechanism of action, benralizumab leads to rapid and near complete depletion of eosinophils and basophils through ADCC (anti-body dependent cell-mediated cytotoxicity), while mepolizumab and reslizumab act through the indirect

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mechanism of eosinophil reduction. There are currently no data directly comparing the implications of MOA differences between the three treatments.

In the absence of further data, we therefore believe it is appropriate to assume equivalent efficacy between benralizumab and reslizumab in the model.

For the relative efficacy of benralizumab compared with mepolizumab, we validated this assumption with a UK clinician, who confirmed that the relative difference between benralizumab and mepolizumab in the ITT population could be assumed to be generalisable to the more severe subgroup. Further, we identified no evidence to suggest the contrary, and this was also the approach taken in the mepolizumab and reslizumab appraisals for comparisons against omalizumab. We therefore believe that this is the most methodologically sound approach in the absence of further evidence, given that both treatments are more efficacious in the more severe subgroup.

A9. Company submission. Please provide further justification for why the differences in trial baseline characteristics for benralizumab and mepolizumab, which the submission acknowledges as 'key differences' (section B.3.3, page162), are not considered sufficient to render MAIC analysis unsuitable (pages.162-163), whereas the differences in baseline characteristics between benralizumab and reslizumab are considered sufficient to render MAIC analysis unsuitable (page 163).

As per NICE TSD 18, a small effective sample size (ESS) indicates highly variable weights, which in turn indicates a lack of population overlap. Also, distributions of weight should be examined directly to diagnose the population overlap.

For the comparison of benralizumab with mepolizumab, a sufficient overlap was present as judged by the distribution of characteristics across the studies, weight distribution, and ESS. The ESS was large enough to obtain reliable effect estimates with sufficient precision (ESS>400 for all scenarios). For the comparison of benralizumab with reslizumab, the overlap between the two populations was very small; after matching, the ESS of the benralizumab trials reduced to 20, equivalent to a 99% reduction. As a result, the effect estimates obtained after adjustment had very large values for standard deviations and hence very low precision.

In light of NICE TSD 18 recommendations and considering a very skewed distribution of weights, and a very low ESS, a MAIC analysis vs. reslizumab was considered unsuitable. Please see appendix pages 353 to 401 for further details.

A10. Company submission, table 51 page 173. Please explain why the odds ratio (OR) is used for 'Patients with complete reduction in mOCS dose' instead of a rate ratio or risk ratio, which would be comparable with the other endpoints.

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The outcome for 'patients with complete reduction in mOCS dose' is a binomial outcome and logistic regression was used to derive the effect estimates and hence, odds ratios with 95% CI were presented. Similarly, for the Poisson outcomes (like annual exacerbation rates) rate ratios with 95% CI were presented.

A11. Company submission, table 50 and 51 page 172-173. Please comment on the negative values for the lower confidence interval of the rate ratio for 'FEV1' (Table 50, page 172) and 'Reduction in Mocs dose' (Table 51, page173), as our understanding is that negative values for rate ratios are illogical.

For 'change from baseline in FEV1' and 'reduction in mean OCS dose from baseline', mean differences with 95% CI were presented (this is specified in figure 25 and figure 26 on pages 122-123 of the main submission dossier). It is an error that these specific tables refer to a 'rate ratio' for these outcomes.

A12. Economic model: Please clarify why change in rescue medication was not used as a clinical input to the model for benralizumab (model file).

The most commonly used rescue medication used for asthma is salbutamol (Ventolin), this costs £1.50 per 200 dose inhaler, or 0.75p per inhalation. Due to its considerably low cost, rescue medication use was not used as a clinical input into the model as it is unlikely to materially impact the results.

Not including rescue medication in the analysis is conservative, as patients using benralizumab require fewer inhalations of rescue medication than those using HD ICS/LABA and therefore will accumulate fewer costs.

Section B: Clarification on cost-effectiveness data

B1. Company submission, section B.3.3. **,** page 162. "Exacerbation rates, quality of life and transition probabilities based on ACQ score) were derived from three benralizumab trials, a pooled analysis of CALIMA and SIROCCO for patients not on mOCS (published and unpublished data) and ZONDA for patients who are on mOCS." Please provide individual patient level (IPD) data used in the analysis, and your analysis.

In relation to the request for individual patient data, AstraZeneca would consider undertaking further analyses with the provision of a protocol and statistical analyses plan, and may consider providing the data if appropriate and after guarantee of safeguarding of the de-identified and anonymised patient data. It should be noted that it is estimated that a request for access to IPD may take several months to action due to internal governance processes.
In general, AstraZeneca does consider legitimate requests for patient level data on a case-by-case basis, following consistent criteria to establish if and how the information provided will be used for valid scientific purposes and to benefit patients.

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The statistical methods concerning the analysis of utilities and health state transitions are detailed below (taken verbatim from the statistical analysis plan):

Utility Analysis

Utility values within each health state will be assessed using a general linear, repeated model. The model will include covariates for:

- Treatment group
- Baseline utility index
- Region (Asia, Eastern Europe, Europe, North America)
- Study (Pooled SIROCCO/CALIMA only)
- Health State
    - Controlled
    - Uncontrolled
    - Exacerbation – OCS burst – prier HS controlled
    - Exacerbation – ER visit – prior HS controlled
    - Exacerbation – Hospitalisation – prior HS controlled
    - Exacerbation – OCS burst – prier HS uncontrolled
    - Exacerbation – ER visit – prior HS uncontrolled
    - Exacerbation – Hospitalisation – prior HS uncontrolled
- Treatment group by health state interaction

The compound symmetry variance/covariance structure will be applied and grouped at the health state level. Least-squares means (LSM) and standard errors of utility will be assessed using the pooled data. The ZONDA data has limited exacerbations requiring ER or hospitalisations, and therefore only the utility for exacerbations requiring an OCS burst will be assessed.
In addition to the modelling approach, summary statistics of the utility values by health states and reporting level will be provided by evaluating the mean of the within patient means.

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Health State

Initially each patient utility value will be allocated to either the controlled or uncontrolled health state based on the ACQ-6 score measured at the same time as the utility value (for even numbers weeks) or the week following the utility value measure (for odd numbered weeks). The exacerbation health state will supersede the controlled/uncontrolled health state and will use include the utility values within ±4 weeks of the exacerbation start date. This window is based on previous analysis undertaken in Golam et al, which found an exacerbation impacts a patient's utility in the windows outlined below:

- OCS burst: 24 days prior to exacerbation start date to, 24 days post exacerbation start date
- ER visit: 31 days prior to exacerbation start date to, 31 days post exacerbation start date
- Hospitalisation: 31 days prior to exacerbation start date to, 38 days post exacerbation start date

Transition probabilities

Transition probabilities will be evaluated by aggregating the 2 weekly transitions between health states. The health state categories assessed will be: controlled, uncontrolled, exacerbation-prior controlled and exacerbation-prior uncontrolled.

Patients will initially be allocated to either controlled or uncontrolled within each post randomisation 2 week cycle, i.e. 0-2 week, 2-4 weeks etc. The controlled and uncontrolled health states will be determined using the ACQ-6 score at the end of each 2-week cycle. The exacerbation health state will be allocated to the 4 cycles which best fit within ±4 weeks of the exacerbation start date, i.e. 8 weeks in total. To implement this, the exacerbation start date will then be adjusted to match the closest cycle start date. The 2 cycles prior to and 2 cycles post the start date will then be defined as exacerbation cycles. Additionally, only the transition into and out of the exacerbation HS will be used, effectively collapsing the 4 cycles per exacerbation, into 1 cycle. The exacerbation HS will be allocated to exacerbation-prior controlled or exacerbation-prior uncontrolled based on the HS controlled or uncontrolled prior to the exacerbation. The exacerbation health state will supersede the controlled and uncontrolled health states.

B2. Company submission, section B.3.4. , page 205. "These values were applied by combining data from the ZONDA trial, data provided by the Observational & Pragmatic Research Institute (OPRI) and condition-specific disutility values from Sullivan et al". Please provide all the data on health-related quality-of-life, and your analysis.

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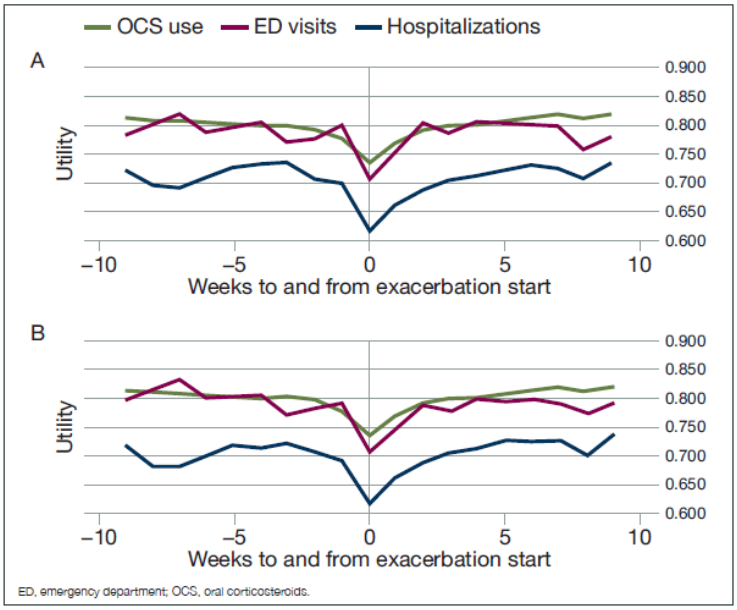
All health-related quality of life data used in this context was taken from the Sullivan paper and has been provided as a reference. No analyses on HRQoL for the adverse events associated with maintenance OCS use have been performed by AstraZeneca.

B3. Company submission, section B.3.3.2., page 166. "Durations across the three exacerbation event types were based on a visual inspection of mean utilities per week. Durations encompassed the week during which the mean utility starts to decline through the week during which the mean utility returns to a stable level." Please clarify how this inspection method was applied, i.e., how 'stable level' was defined.

'Stable level' was not given a numerical value. It was determined based on the reader's assessment of the figure below; and is described in more detail below.

There was no systematic method used for the visual inspection. Because of this, readers may differ in their estimates of exacerbation durations, especially for ED visits which fluctuated considerably due to limited data. The graphs and our selected durations are shown below:

Figure 2. A) Grand Mean Utilities and B) Mean of Averages Utilities Plots



Duration to calculate grand mean (Weeks)

OCS burst: -3, +3

ER: -4, +4

Hospitalised: -3, +6

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Duration considered to calculate mean of averages

OCS burst: -3, +3

ER: -4, +4

Hospitalised: -3, +5

For patients having had an exacerbation, we have considered week 0 to be the starting point of a clinically defined exacerbation and then we have investigated backwards to the point where the weekly utility started to decline (closest week for which the utility weekly value is smaller than the utility weekly value for the week before). The initial point of decline we have considered as the point at which the patient begun to experience the quality of life impact of an exacerbation. We did the same in the forward weeks after week 0, so that the closest week where the utility value is larger than the utility value for the week thereafter is selected as the end week.

Section C: Textual clarifications and additional points

C1. Please correct “reference source not found” errors in the submission.

These errors are a product of cross-references to the separate Appendix document (as the main document and appendices were originally both in one document, and were separated prior to submission). The errors should not appear on-screen, as long as the reader does not update fields. If the errors appear when printing, correct this by going to Word options ► display ► uncheck ‘update fields before printing’. If this does not solve the problem, you can convert fields to plain text by selecting all (Ctrl+A), then pressing Ctrl+Shift+F9. If you are still experiencing issues, we would be happy to send a revised version with field codes reverted to text.

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Patient organisation submission

Benralizumab for treating severe asthma [ID1129]

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.

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	[redacted]
2. Name of organisation	Asthma UK
3. Job title or position	Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Asthma UK is the UK's leading asthma charity. We support people with asthma when they need us the most and fund world-leading research to find better treatments and ultimately a cure. Our goal is to prevent asthma attacks, especially those that result in emergency hospitalisation and death.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Asthma UK receives no funding from the tobacco industry.
5. How did you gather information about the experiences of patients and	Information about the experiences of patients and carers was gathered through our helpline, social media interactions with people with asthma and past Asthma UK publications.

carers to include in your submission?	
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?	Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment. Severe asthma affects nearly 5% of people with asthma – around 250,000 people in the UK, of whom a subgroup of around 40% will have an eosinophilic phenotype.[1][2][3] The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma.[4] Severe eosinophilic asthma is a specific type of asthma, rather than simply an extreme form of the condition. It does not respond to standard treatment and requires more intensive therapies to control symptoms to prevent attacks, hospitalisations and deaths. People with the most severe asthma represent a specific challenge: they not only suffer greater morbidity, but they also fall outside the robust evidence-base that informs most asthma care, requiring specialist attention, treatment and pathways.[5] Ongoing severe symptoms and a complex medicine regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions lead to further social

[1] Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178:218-224.
[2] Hekking PP, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. Journal of allergy and clinical immunology. 2015;135:4
[3] S chleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. BMC Pulmonary Medicine. 2013;13:11. doi:10.1186/1471-2466-13-11.
[4] Royal College of Physicians. Why asthma still kills: The National Review of Asthma Deaths; 2014.
[5] Wenzel S. Characteristics, definition and phenotypes of severe asthma. In: Chung KF, Bel E, Wenzel S, editors. ERS Monograph: Difficult-to-Treat Severe Asthma. 51: European Respiratory Society; 2011.

	isolation and economic disadvantage for people affected by asthma as well as high costs to the NHS.[6] [7] The costs for people on maintenance oral corticosteroids were 43% higher and where people had two or more exacerbations and oral corticosteroid courses the costs are 31% higher than those with less than two courses of treatment with oral corticosteroids[8]. Overall, the costs are significantly higher than for people with controlled asthma which a recent study estimated at £451 per person, per year.[9] **Experiences of people living with severe asthma** "Life with severe asthma is limiting. There's no spontaneity because everything I do is timed by when I need to use my nebulisers, and I'm always planning ahead. I have a wide range of triggers – dust mites, tree moulds, pollen, temperature changes, exercise, smoke, and rapeseed – so I'm very organised when it comes to my managing my asthma. Whenever I go out I need to make sure I take my asthma medicines half an hour beforehand." *Julia Kerr, 29 years old*[10] "I was diagnosed with severe asthma after several years of struggling to keep my symptoms under control. I was using my reliever inhaler more than usual, despite taking my preventer as prescribed, having frequent asthma attacks and taking courses of steroids several times a year. In 10 months alone I

[6] D'Amato, Gennaro, et al., "Treating severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab): a review." *Multidisciplinary respiratory medicine* 9.1 (2014): 23.
[7] Bajorek, Hind & Bevan (2016) The Work Foundation: The Impact of long term conditions on employment and the wide UK economy
[8] O'Neill et al, 2016, Thorax http://dx.doi.org/10.1136/thoraxjnl-2013-204114
[9] Ibid
[10] https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/julia-kerr/ (accessed: 04/01/18)

had 12 emergency hospital admissions and was seeing my GP at least once a week for a nebuliser." *Callie-Anne, 31 years old*[11]

Experiences of carers for people with severe asthma

The impact on everyday relationships was also highlighted in Asthma UK's report *Fighting for Breath*[12]:

"With the constant need to make compromises for severe asthma, relationships can suffer…The impact of caring for someone with severe asthma is substantial – many parents struggle to maintain a job because their child needs their support. This doesn't just affect parents – other family members, or even children can also be carers. Sadly, because asthma isn't usually seen as something that has a big impact, those who spend a lot of time caring for people with severe asthma get even less recognition and support than other carers."

"It can be hard to tell when asthma attack is coming on. We've not been able to identify specific triggers, so it's like suddenly, the asthma totally takes over. And this year, Jack had his worst asthma attack yet. It was a glorious Sunday afternoon in June, everyone was enjoying the sun. I'd been out for an hour or so when I got a call from Jack's older sister, who told me he'd come downstairs asking for an ambulance. I rushed home, and we waited 45 frantic minutes for it to arrive. We hadn't even pulled out of my street when Jack stopped breathing and lost consciousness. I was so scared but I tried to keep it together and

[11] https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/sex-and-romance-callie-anne/ (accessed: 04/01/2018)
[12] Asthma UK. Fighting for Breath; (2011): 14

	not be the crazy emotional mum so that the paramedics and doctors could work their magic. And yet, at one point, it looked like Jack's heart stopped." *Fiona, mother of 12-year-old Jack*[13]
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The existing treatments for severe asthma are extremely limited. Patients predominantly rely on oral corticosteroids to control symptoms, which cause toxic and debilitating side effects, particularly when taken for long periods, which in the case of severe asthma they often are. A survey into the side effects of oral steroid use by people with asthma was conducted by Asthma UK in 2016. Various side effects were determined, including 56.4% reporting weight gain; 37% reported feeling more anxious and 33% reported aching and cramping muscles and joints. A study by Sweeney et al., presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry) and shows that OCS use results in a higher prevalence of comorbidities - including type II diabetes, hypertension and osteoporosis.[14] This should be factored into any calculations made to determine benralizumab's incremental cost-effectiveness ratio (ICER), in addition to quality-of-life benefits to carers. The side effects and ineffectiveness at reducing severe asthma symptoms in patients are significant contributors to low adherence rates.[15]

[13] https://www.asthma.org.uk/advice/child/parent-stories/what-its-like-to-have-a-child-with-severe-asthma/ (accessed: 04/01/2018)
[14] Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016; 71:339-346 doi:10.1136/thoraxjnl-2015-207630
[15] Asthma UK. Severe Asthma: the unmet need and the global change; (2017): 5

	The introduction of biologics to treat asthma has proved to be life-transforming for people with severe asthma who are eligible for them. For example, Jane Farmilo, who was diagnosed with severe eosinophilic asthma and started taking mepolizumab said “Two weeks after my first injection I could climb hills in the Peak District. After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I’m actually thinking about increasing the number of hours I do. This treatment has really transformed my life.”[16] A further example, Jenny Negus who was diagnosed with severe asthma and treated with omalizumab said "My asthma has a tendency to screw up many things! This holiday is just one example. Very luckily the owner of the farm heard about our ruined trip and gave us a heavily discounted price on a weekend away there later that year - every cloud hey!... And since having monthly Xolair injections to reduce my allergic response, at least I'm able to go outside in summer now.”[17] Though existing biologics have offered relief of symptoms to some, they are limited in that they are only made available to a specific sub-population. As such, the approval of a new biologic offers an opportunity to help more people with severe asthma for whom the treatment is appropriate.
8. Is there an unmet need for patients with this condition?	There is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with very poor side effect profiles and can have damaging effects if taken over long periods of time. These

[16] Asthma UK. "Life-changing new treatment." *Asthma Magazine.* Jan 2018: 8-9. Print.
[17] https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/how-i-cope-with-severe-asthma/ (accessed: 04/01/2018)

	side effects include sleeplessness, anxiety, weight gain, and corticosteroid-related comorbidities such as osteoporosis, hypertension and cataracts.[1819] These side effects contribute to an increased rate of sickness absence for people with asthma. In Europe, one in four patients with asthma report missing at least one day of work as a result of their condition each year, whilst 14% report losing over 12 working days.[20] With all the potential side effects, oral corticosteroids offer little help to people with severe asthma. Despite adhering to current recommended asthma treatment including oral corticosteroids, symptoms can persist and their asthma can remain uncontrolled, putting them at risk of potentially life-threatening attacks.[21] The wider impacts that severe asthma has on their life include depression, anxiety and fear of social rejection or loss of employment.[22] As such, benralizumab could provide an (additional) alternative option for people with severe eosinophilic asthma responding poorly to steroids. Further, the IDEAL study, through a comparison of the eligibilities for mepolizumab, reslizumab and omalizumab demonstrated that the available biologics mostly serve different severe asthma populations despite some minimal overlap[23]. This goes to provide further weight to the case for introducing an additional biologic as a treatment for severe asthma.

[18] Asthma UK. Severe Asthma: the unmet need and the global change; (2017): 10
[19] https://www.aaaai.org/global/latest-research-summaries/New-Research-from-JACI-In-Practice/oral-corticosteroid (accessed: 05/01/2018)
[20] Bajorek, Hind & Bevan (2016) The Work Foundation: The Impact of long term conditions on employment and the wide UK economy
[21] Asthma UK. Severe Asthma: the unmet need and the global change; (2017): 8
[22] Ahmad, Sohail, and Nahlah Elkudssiah Ismail. "Stigma in the lives of asthma patients: a review from the literature." International Journal of Pharmacy and Pharmaceutical Sciences 7, no. 7 (2015): 40-46.
[23] Albers, Frank, et al. "Eligibility for Mepolizumab, Omalizumab and Reslizumab in the EU population: The IDEAL study." (2016): PA4216.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Unfortunately, we have not yet been able to get views from people with severe eosinophilic asthma that have been treated with benralizumab or their carers.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Unfortunately, we have not yet been able to get views from people with severe eosinophilic asthma that have been treated with benralizumab or their carers.
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.	Around 250,000 people are estimated to have severe asthma, of which a subgroup of around 40% will have an eosinophilic phenotype[24]. This new treatment is specifically targeted to reduce severe asthma attacks by reducing the levels of blood eosinophils associated with the condition. It is therefore logical that this subgroup of people with severe asthma could potentially benefit more than the broader severe asthma group.

[24] Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. BMC Pulmonary Medicine. 2013;13:11. doi:10.1186/1471-2466-13-11.

	As benralizumab is targeted at reducing the levels of blood eosinophils associated with severe asthma, those with severe asthma who do not have an eosinophilic phenotype would benefit less from the treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	n/a
Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Severe asthma affects nearly 5% of people with asthma – around 250,000 people, of whom a subgroup of around 40% will have an eosinophilic phenotype that might benefit from benralizumab. • People with severe asthma do not respond to standard inhaled asthma treatment and require more intensive treatments to control their asthma symptoms, prevent attacks, hospitalisations and deaths. • There is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with very poor side effect profiles. They endure numerous rounds of oral corticosteroids and are subjected to damaging side effects, for example diabetes and osteoporosis. • Benralizumab could provide an alternative option for people with severe eosinophilic asthma that do not respond well to existing treatment options in that, their symptoms persist, and their asthma remains uncontrolled.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Benralizumab for treating severe asthma [ID1129]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The British Thoracic Society**

3. Job title or position	**Chair Specialist Advisory Group Asthma. BTS**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The British Thoracic Society (BTS) exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee. Our activities cover all of the UK. We seek to work collaboratively with others and maintain a global outlook.**
5b. 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,	Main aim is to reduce the number of exacerbations of asthma in severe difficult to control asthmatics.

or prevent progression or disability.)	
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 clinically important exacerbations of asthma in a year. Improvement in lung function. Reduction in use of oral corticosteroids.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are other biologic therapies available for this condition that have similar modes of action to reduce eosinophils. There is a need for more effective treatments,
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The condition is usually treated with either oral corticosteroids of other monoclonal antibodies such as omalizumab, mepolizumab or reslizumab.
• Are any clinical guidelines used in the treatment of the	There are guidelines on the management of asthma produced by The British Thoracic Society / SIGN that cover this severity of asthma. There are also NICE guidelines on the management of asthma although

condition, and if so, which?	biologic therapy is not covered in the guideline. There are recommendations for Omalizumab, Mepolizumab and Reslizumab available with NICE.
• 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.)	Pathways are well defined. NHSE specialist commissioning ensures that patients suitable for this treatment are seen in specialist commissioned centres by those with expertise and experience in assessing severe asthma.
• What impact would the technology have on the current pathway of care?	The technology would give further options for treatming patients with severe difficult to control asthma where the only option would be oral corticosteroids.Therefore this technology would have steroid sparing properties.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. As per other biologics for asthma.
• How does healthcare resource use differ between the technology and current care?	Same as for other existing biologics.
• In what clinical setting should the technology be	Secondary care use following specialist commissioned services assessment in a specialist clinic.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The infrastructure already exists for those giving biologic therapy so this should be minimal.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	This is unknown. Studies were not designed with this in mind. However theoretically this could be the case is an exacerbation of asthma is a risk factor for death from such an event. Any reduction in the number of exacerbations could be interpreted as reducing the possibility of death and therefore increasing the length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with severe asthma. Eosinophilic phenotype.
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.)	Similar to current care with biologic therapy.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Biologic therapy is given following assessment by specialist centres. Usually once current treatment has been optimised and compliance assessed. Centres will have been approved through NHSE specialist commissioning
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 alternative treatment would be to use long term oral corticosteroid therapy with its associated unwanted adverse effects such as weight gain, skin thinning, increased risk of infection, osteoporosis, cataracts, gastritis and osteonecrosis amongst others. The reduced incidence of these effects would not be captured in a QALY.
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	Yes it is innovative in its particular action on the IL5 receptor although the effect of reducing eosinophils is not. As above it improves the way this is met by giving an alternative to oral corticosteroid therapy.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This adds to the options for biologic therapy at this severity of asthma
• Does the use of the technology address any particular unmet need of the patient population?	Yes but there are other options with different mechanisms.
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 technology will need to be given by injection and this will have detrimental effects with pain and also the inconvenience of visits to a healthcare centre to be given.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes for other biologics

• 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?	Reduced exacerbations, improved quality of life, improved symptoms and lung function Yes
• 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?	Not known
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Not yet available
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- New option for biologic therapy
- Steroid sparing effects
- Specialist commissioned services controlled
- Improves exacerbation rates, quality of life and lung function
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Benralizumab for treating inadequately controlled asthma

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Tim Harrison**
2. Name of organisation	**University of Nottingham**

3. Job title or position	**Professor/Honorary Consultant**
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 this condition? ☒ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. 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 improve control of severe asthma, including a reduction in the use of systemic steroids
8. 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.)	Improvement in ACQ by 0.5 or more, 30% reduction in exacerbations requiring systemic steroids or 50% reduction in maintenance systemic steroids.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, we have to resort to using systemic steroids and many patients remain poorly controlled despite this.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	High dose inhaled medication, with bursts or maintenance systemic steroids. Some patients are suitable and benefit from omalizumab or an IL-5 antagonists.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, BTS/SIGN and GINA guidelines
• 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.)	Clear pathways of care as described in asthma guidelines and NHS England severe Asthma commissioning. Minimal differences in opinion now.
• What impact would the technology have on the current pathway of care?	Increase the number of patients receiving a monoclonal antibody and therefore improving morbidity from the disease and adverse effects of prednisolone.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, very similar to how the other IL-5 antagonists are used.

• How does healthcare resource use differ between the technology and current care?	No major difference for patients already receiving a biological treatment, although benralizumab requires less frequent injections and therefore hospital attendances.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist severe asthma services.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal. Outpatient space and nurse training to administer safely.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, less impact on time for treatment and potentially greater reduction in systemic steroid use.
• Do you expect the technology to increase length of life more than current care?	Not compared with other IL-5 antagonists but possibly against other care mainly due to a reduction in systemic steroid use.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective in those with active eosinophilic inflammation
The use of the technology	
14. 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	Easier as injections only required every 8 weeks rather than every 2-4 weeks.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment will require confirmation of severe asthma plus a raised blood eosinophil count. Stopping is less easy but likely to be similar to the criteria for mepolizumab and resilizumab.
16. 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
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Major impact over established care but impact over and above mepolizumab less dramatic

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?	Il-5 antagonists are a step-change, but the benefits of benralizumab over mepolizumab/resilizumab cannot really be described as a step-change.
• Does the use of the technology address any particular unmet need of the patient population?	Good data for oral steroid reduction which is a very important aim of severe asthma management.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects seen to date are minor and far less than those seen with oral steroids.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• 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?	Exacerbation and oral steroid reduction
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 431 (mepolizumab) and NICE technology appraisal guidance 479 (reslizumab)?	The possibility of incomplete eosinophilic inflammation in the lungs being reported with mepolizumab but no firm trial data reported yet.
22. How do data on real-world experience compare with the trial data?	No real-world evidence currently available
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is it reasonable to assume clinical equivalency between reslizumab and benralizumab? Is the company's assumption that all clinical values and therefore transition probabilities are equivalent appropriate?	Yes
25. In the absence of patient level data in the public domain for the clinical effectiveness of mepolizumab in the NICE recommended severe eosinophilic asthma subgroup, is it reasonable to assume that	Yes

the relative effectiveness of benralizumab and mepolizumab in the intention to treat population will be replicated in the severe eosinophilic asthma sub-group (blood eosinophil count ≥300 cells per µl, AND either ≥ 3 prior asthma exacerbations for benralizumab [≥4 for mepolizumab] needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months?	
Key messages	

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Good data for exacerbation reduction
- Good data for oral steroid reduction
- Superior eosinophil count reduction
- 8 weekly dosing important for patients
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Benralizumab for treating inadequately controlled asthma

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Shuaib Nasser**
2. Name of organisation	**Royal College of Physicians**

3. Job title or position	**Consultant in Allergy and Asthma**
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 this condition? ☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. 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 improve control of eosinophilic asthma by reducing exacerbations and requirement for systemic corticosteroids. In addition to reduce the impact of co-morbidities ie chronic rhinosinusitis, recurrent nasal polyps and adverse effects associated with corticosteroid use.
8. 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 asthma exacerbation rate, hospital admissions and corticosteroid use by 30-50%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes the use of oral corticosteroids remains unacceptably high in asthma
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Repeated use of systemic corticosteroids, maintenance systemic corticosteroids in the most severe, emergency hospital admissions and use of multiple classes of asthma meds
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BTS/SIGN/ GINA/ NICE
• 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.)	Well defined pathways of care in guidelines and NHSE commissioned services although differences persist although improving
• What impact would the technology have on the current pathway of care?	Reduce exacerbation rates and hence admissions and use of systemic corticosteroids. Also add to currently approved anti-eosinophil biologics mepolizumab and reslizumab although this drug has different mode of action and after the first three months can be administered every 2 months.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes using well defined treatment pathways / services already in place for other biologics

• How does healthcare resource use differ between the technology and current care?	Less frequent administration ie after the first three months can be administered every 2 months
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	NHSE commissioned specialist asthma services will initiate therapy and then continued in asthma services in secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Expansion of existing services as numbers increase although this is currently happening with use of mepolizumab
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Less frequent administration costs and disruption to patient's lives but overall similar benefit to currently used biologics
• Do you expect the technology to increase length of life more than current care?	By reducing use of systemic corticosteroids but not compared to other anti-eosinophil drugs. However reduced frequency of administration may improve compliance and take up

• Do you expect the technology to increase health-related quality of life more than current care?	Not compared to other anti-eosinophil drugs. However reduced frequency of administration may improve compliance and take up and hence QOL
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This drug is effective eosinophilic asthma and those with frequent requirements and good response to systemic corticosteroids
The use of the technology	
14. 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	Less frequent administration will reduce visits to hospital and NHS costs and therefore disruption to patient's lives ie every 8 wks rather than every 4wks

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initiation of therapy only by NHSE commissioned centres using similar rules applied for mepolizumab
16. 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 reduced use of systemic corticosteroids will reduce long-term morbidity and early mortality AND improvements in rhino sinusitis and requirements for frequent surgery for nasal polyps in the subset of patients with these conditions
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Highly innovative in mode of action although efficacy likely to be similar to mepolizumab and reslizumab

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?	only in mode of action although mepolizumab as first anti-eospinophil drug was the real step-change and efficacy of benralizumab likely to be similar to mepolizumab / reslizumab
• Does the use of the technology address any particular unmet need of the patient population?	Reduction in exacerbation, use of systemic corticosteroids,
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	So far appear to be minimal but repeated long-term administration may have an effect on QOL
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• 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?	Reductions in exacerbations, use of systemic corticosteroids, improvements in QOL and FEV1. Minimal effects on hospital admissions may have been due to few admissions at baseline
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Very likely to if there are reductions in use of systemic corticosteroids
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 431 (mepolizumab) and NICE technology appraisal guidance 479 (reslizumab)?	no
22. How do data on real-world experience compare with the trial data?	Not aware of any published
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Is it reasonable to assume clinical equivalency between reslizumab and benralizumab? Is the company's assumption that all clinical values and therefore transition probabilities are equivalent appropriate?	Yes
25. In the absence of patient level data in the public domain for the clinical effectiveness of mepolizumab in the NICE recommended severe eosinophilic asthma subgroup, is it reasonable to assume that	Benralizumab is most effective in those with most exacerbations / reliance on OCS and therefore ≥4 exacerbations is likely to be the optimal group and also allow uniformity when delivering the pathway of care to these patients

the relative effectiveness of benralizumab and mepolizumab in the intention to treat population will be replicated in the severe eosinophilic asthma sub-group (blood eosinophil count ≥300 cells per µl, AND either ≥ 3 prior asthma exacerbations for benralizumab [≥4 for mepolizumab] needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months?	
Key messages	

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Efficacy data similar to mepolizumab and reslizumab
- Reduced administration costs and disruption to patient lives with 8 wkly regimen
- Unique mode of action via ADCC leading to more complete eosinophil depletion – which may have advantages
-
-

Thank you for your time.

Pleas`e log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Benralizumab for treating severe asthma [ID1129]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- 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	**Lehanne Sergison**
2. Are you (please tick all that apply):	a patient with the condition? YES a carer of a patient with the condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation	Asthma UK
4. Did your nominating organisation submit a submission?	yes, they did YES no, they didn't I don't know
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 YES no, I disagree with it I agree with some of it, but disagree with some of it other (they didn't submit one, I don't 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.)	
7. How did you gather the information included in your statement? (please tick all that apply)	I have personal experience of the condition YES I have personal experience of the technology being appraised I have other relevant personal experience. Please specify what other experience: I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	

8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Asthma, especially in the most severe form can be very debilitating, isolating and frustrating. Symptoms can change from day to day, hour to hour, I have experienced incidents where I have been relatively well and been intubated within a matter of hours. Asthma can be unpredictable and burdensome. I had to give up my career, which resulted in significant financial constraints. Planning activities can be difficult because of the nature of the disease, this may be because of exposure to allergens, pollution or just having to cancel because it's a bad day! Friends are lost, relationships breakdown and the isolation and depression grows. The brain is willing but generally the simplest tasks can be exhausting, even talking can be challenging sometimes. Guilt floods your emotions, you feel that you are letting others down and maybe not trying hard enough! Life becomes a routine of physiotherapy, taking medicine and hospital visits. Asthma symptoms are often invisible, tightness in your chest, breathlessness, wheezing, coughing, fatigue, insomnia and even pain. These symptoms are often compounded by the side effects from the drugs taken to combat the disease, often type II diabetes, psychosis, osteoporosis, resulting in more medication and hospital visits. Onlookers are frequently quick to judge assuming that you are a smoker and that your symptoms are self inflicted, moreover they are of the belief that it can be simply remedied with a blue inhaler. Severe asthma can give you a sense of vulnerability and worthlessness. Coping techniques are mastered, peer support groups develop and life goes on, the struggle continues and you do what you can to be relevant, to survive. You take medicines that cause weight gain and mood to swings, you become grateful for the use of a wheelchair/mobility scooter, the portable nebuliser and oxygen because it enables a sense of normality.
Current treatment of the condition in the NHS	

9. What do patients or carers think of current treatments and care available on the NHS?	Available care in the NHS is a lottery, largely dependent upon the competency of your GP, local A&E and Chest Consultant. I am fortunate with my GP and Consultant but visits to my local A&E and hospital can be daunting even harrowing. Treatment options are limited and can cause significant co-morbidities, I for one have developed osteoporosis, epilepsy, type II diabetes to name but a few. Despite being on maximal treatment, I am still very symptomatic and regularly hospitalised.
10. Is there an unmet need for patients with this condition?	Yes. Patients are still suffering, just about managing, the burden of asthma is not simply limited to the patient but to the wider family, the economy and the NHS. Patients with asthma are still dying.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	In recent year there have been two new drugs mepolizumab and reslizumab but these will not suit all of the severe asthma population, benralizumab needs to be made available to meet the needs of this sub-set of patients. I also understand that the drug is administered sub-cutaneously every two months which would be more favourable to both patients and clinicians. If the drug is effective, it should enable patients to enjoy a better quality of life, be less symptomatic and reduce their reliance on oral corticosteroids.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Benralizumab will only be available in specialist centres which may be a barrier to some patients accessing the medicine.
Patient population	

13. 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.	Yes the patients that meet the criteria regarding the eosinophils levels and oral corticosteroid use may benefit from the new medicine, those who do not meet the criteria will not benefit.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Living with severe asthma is debilitating and impacts widely on families and society
- Treatment options for severe asthma are limited
- The side effects from oral corticosteroids can significantly add to the burden of the disease
- Severe asthmatics make up approx 5% of the asthma population but these patients utilise a disproportionate amount of resources
- Despite other biologicals being available, they are not suitable for all patients, Benralizumab will widen treatment options and hopefully improve the lives of many.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Benralizumab for treating severe asthma [ID1129]
Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Asthma UK and consequently I will not be submitting a personal statement.

Name: Dr Samantha Walker

Signed:

Date: 20/03/2018

Benralizumab for treating severe asthma

A Single Technology Appraisal

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU

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Contributions of authors

Irina Tikhonova	Provided overall project management and management of the economic modelling team, led the critique of the company's decision problem and cost-effectiveness evidence, wrote the decision problem and background sections, contributed to writing of the cost-effectiveness section and collation of the report.
Linda Long	Provided project management of the clinical evidence team; led the critique of the clinical evidence; critiqued the methods of review(s) and the safety analysis and wrote the corresponding sections of the report; contributed to the writing and editing of the report.
Neel Ocean	Led the critique of the economic model; checked/corrected the model and added ERG-specific controls; and wrote the corresponding sections of the report.
Max Barnish	Performed detailed statistical critique of matched-adjusted indirect comparison (MAIC) analyses; wrote section of report on MAIC analyses; edited the report; collated clinical effectiveness chapter for draft report; and collated the final report.
Sophie Robinson	Wrote the sections of the report relating to the literature searches.
Elham Nikram	Contributed to the critique of the company's submission, parameterisation and checking of the PenTAG independent economic assessment, and editing of the ERG's report.
Segun Bello	Critiqued the clinical effectiveness analysis for the three pivotal trials and wrote the corresponding section of the report.
Sophie Dodman	Contributed to the quality assessment section of the report.
David Halpin	Provided clinical advice on severe asthma and its management within the NHS; reviewed and revised a draft version of the report.
Martin Hoyle	Project director and oversight of the project. Contributed to the editing of the report.

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Abbreviations

ACQ	**Asthma Control Questionnaire**
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AER	Annual asthma exacerbation rate
AI	Auto-injector
ALT	Alanine transaminase
AQLQ	Asthma Quality of Life Questionnaire
AQL-5D	Asthma quality of life: 5 Dimensions
AR	Adverse reaction
AST	Aspartate transaminase
ASUI	Asthma Symptom Utility Index
BEN	Benralizumab
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BTS	British Thoracic Society
CE	Cost-effectiveness
CENTRAL	Central Register of Controlled Trials
CGIC	Clinician global impression of change
CI	Confidence interval
CIC	Commercial in confidence
CIQ	Classroom Impairment Questions
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DALY	Disability-adjusted life-year
DOF	Data on file

DRMI	Dropout reason-based multiple imputation
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ED	Emergency department
EMA	European Medicines Agency
EOS	Eosinophils
EQ-5D	EuroQol 5-Dimensions instrument
ER	Emergency room
ERG	Evidence Review Group
ERS	European Respiratory Society
ESS	Effective sample size
EU	European Union
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FU	Follow-up
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General practitioner
HES	Hospital episode statistics
HRQOL	Health-related quality of life
HS	Health state
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IL	Interleukin
IP	Investigational product
IPD	Individual patient data

IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice-response system
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic receptor antagonist
LCI	Lower confidence interval
LS	Least squares
LTRA	Leukotriene receptor antagonist
LY	Life-year
LYG	Life-years gained
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
MCID	Minimum clinically important difference
MD	Mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEPO	Mepolizumab
MI	Myocardial infarction
MOA	Mechanism of action
NA	Not applicable
NC	Not calculable
NCT	Clinical trial registry number
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIS	Nationwide Inpatient Sample
NK	Natural killer
NMA	Network meta-analysis
NO	Nitric oxide

NR	Not reported
NRAD	National Review of Asthma Deaths
NSS	Not statistically significant
OCS	Oral corticosteroid
OPCRD	Optimum Patient Care Research Database
OR	Odds ratio
PAS	Patient access scheme
PEF	Peak expiratory flow
PGIC	Patient Global Impression of Change
PICOS	Population, Intervention, Comparator, Outcomes criteria
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q(X)W	Every (X) weeks
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RESLI	Reslizumab
RR	Relative risk
SABA	Short-acting beta-agonist
SC	Subcutaneous
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SOC	Standard of care
SCS	Systemic corticosteroid
SE	Standard error
SPC	Summary of product characteristics

STA	Single technology appraisal
STC	Simulated treatment comparison
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UCI	Upper confidence interval
UK	United Kingdom
VAS	Visual analogue scale
WHO	World Health Organisation
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay

1 Summary

1.1 Critique of the decision problem in the company submission

The company's submission (CS) generally reflected the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The scope considered adults with severe asthma with elevated blood eosinophils. The CS, however, focused on part of the technology's marketing authorisation: a NICE recommendation was sought for the subgroup of adults with severe eosinophilic asthma that is inadequately controlled, despite high-dose inhaled corticosteroids (ICS) (≥ 800µg FP daily) plus long acting β-agonists (LABA) with:

- A blood eosinophil count that has been recorded as 300 cells per µL or more

AND either

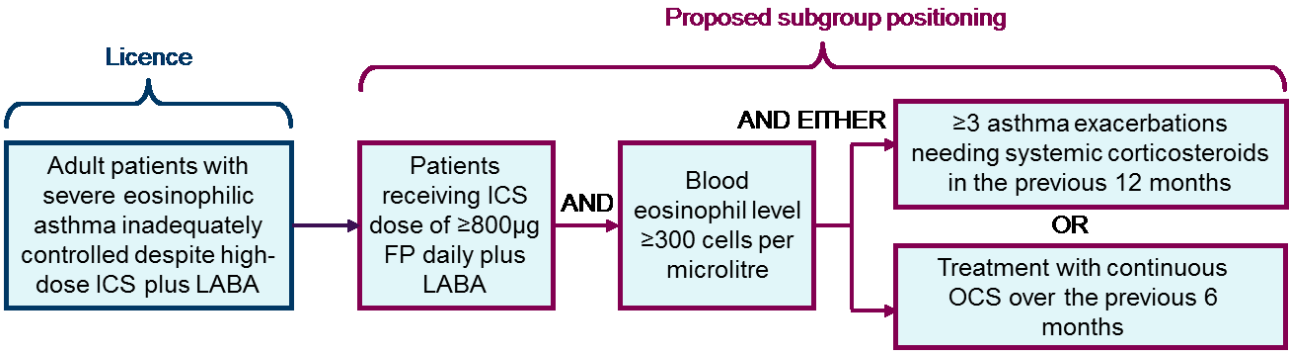
- 3 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months

OR

- Treatment with continuous oral corticosteroids over the previous 6 months

The proposed subgroup reflects where benralizumab provides the most clinical benefit based on results from Phase 3 trials (SIROCCO, CALIMA and ZONDA). As stated in the CS, benralizumab would fit into the existing NICE asthma pathway within the 'difficult or severe asthma' patient category under the 'asthma management' section. Figure 1 shows the proposed sub-group positioning for benralizumab (BEN) where a recommendation is sought.

Figure 1 Context of benralizumab in the clinical context of care



Source: Fig. 12, p. 58, CS

The outcomes of the economic analysis were in line with the scope, with the following exceptions:

- Patient evaluation of response was not available in the trial data
- Discontinuation was treated as a constant rather than a time dependent variable, as is consistent with other appraisals in severe asthma.

1.2 Summary of clinical effectiveness evidence submitted by the company

Three pivotal regulatory trials (SIROCCO, CALIMA and ZONDA) informed the comparison for benralizumab vs. SOC. These trials demonstrated that benralizumab is effective at reducing asthma exacerbations versus placebo when added to SOC (by 43% [RR: 0.57; 95% CI: 0.47-0.69; p<0.0001] in a pooled analysis of SIROCCO/CALIMA, and by 70% in ZONDA [nominal p<0.001]); reducing the use of oral corticosteroids (OCS) with a 75% median reduction in OCS dose compared with 25% for placebo (p<0.001), and a 4-times higher odds of achieving a reduction in OCS dose in ZONDA; and improving asthma symptoms.

A subgroup analysis was performed for patients with severe eosinophilic asthma that is inadequately controlled, despite high-dose ICS plus LABA, with a blood eosinophil count ≥300 cells per µl, AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months. From the pooled subgroup analysis of SIROCCO/CALIMA based on the population per NICE scope, benralizumab demonstrated a significant reduction in the annual asthma exacerbation by 53% (RR = 0.47; 95% CI 0.32 – 0.67: p < 0.001) and a reduction in AER in ZONDA trial by 75% (RR = 0.25; 95% CI 0.13 – 0.47: p < 0.001). The reduction in AER for the pooled subgroup analysis was similar to that from the ITT analysis of the SIROCCO trial (51%) but higher than AER reduction from the ITT analysis of the CALIMA trial (28%). Rate of exacerbation associated with ER visits was also reduced by 69% (RR = 0.31; 95% CI 0.09 – 1.01: p = 0.51) but not with hospitalisation (RR = 1.01; 95% CI 0.30 – 3.45: p = 0.988), in the pooled analysis.

[redacted]

In the absence of head-to-head data versus mepolizumab, a matched indirect comparison (MAIC) adjusting for trial differences was conducted. It showed

[redacted]

[redacted] A MAIC versus reslizumab was considered in the absence of head-to-head data, but was not considered feasible due to significant differences between trial baseline characteristics. Therefore, equivalent efficacy was assumed for benralizumab and reslizumab in exacerbation reductions and ACQ transitions without evidence to support it. OCS-sparing data for reslizumab were not available. In terms of safety outcomes, benralizumab was found to be well tolerated, with rates of AEs, serious AEs, and AEs leading to discontinuation of treatment being similar between the benralizumab and placebo groups. Most AEs were mild to moderate in intensity, and not considered to be related to treatment.

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The ERG believed the analysis of the key pivotal trials, SIROCCO, CALIMA and ZONDA, to be adequate. The ERG noted that data in the main analysis for CALIMA and SIROCCO trials also included patients with two baseline AER in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations).

The company noted that reductions in exacerbation rates were observed to be greater in the SIROCCO trial than in the CALIMA trial and suggested that the observation might be due to three key drivers; regional effect, exacerbation history, and background medication. The ERG considered it is likely that the difference in magnitude of treatment effect is related to unknown confounders.

The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both SIROCCO and CALIMA trials only for the Asian population.

The ERG believed that the pooling of the subgroups from the CALIMA and SIROCCO trials was appropriate.

[redacted]

While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted].

Benralizumab appeared to be well tolerated with an adequate safety profile in the short term (up to one year). The most common reported side effects include worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis although these occurred at similar rates compared to placebo.

The CS stated that one patient in the benralizumab arm died due to AEs, which was not considered to be study drug-related. However, the ERG noted that [redacted].

The ERG noted that the safety profile obtained from the CS pivotal RCTs was based on trial data with patients concurrently treated with oral corticosteroids. The ERG noted that the CS did not look to include observational studies assessing the safety of benralizumab.

While no cases of anaphylaxis were observed in SIROCCO or CALIMA, the ERG noted that patients were excluded from the SIROCCO and CALIMA trials if they had a history of anaphylaxis with any biologic drug. It has been reported in the literature that anaphylaxis may occur rarely (0.3%) after exposure to reslizumab and the ERG suggest further studies are needed to establish risk of anaphylaxis for benralizumab for people with no prior exposure to any biologic drug.

The ERG noted the absence of trial data to establish the risks of benralizumab on malignancy and safety in the medium to long term as well as during pregnancy.

The MAIC analysis was largely conducted according to NICE DSU recommendations. However, AstraZeneca declined the ERG request to provide individual patient data (IPD) within the time frame of the appraisal, precluding the ERG from checking the clinical analysis which incorporated a considerable amount of unpublished data. Therefore, the ERG could not be sure that the assumptions underpinning the analysis were appropriate.

The ERG had some concerns about the methodology of the MAIC analysis. There was evidence of selective outcome reporting, whereby outcomes [redacted]. The effect modifier selection process for the MAIC analysis excluded effect modifiers that were not in imbalance between the benralizumab and mepolizumab trials, contrary to NICE DSU recommendations. Data were imputed from one technology to another despite benralizumab having a fundamentally different mechanism of

action from mepolizumab and reslizumab. No clinical analysis was conducted to compare benralizumab and reslizumab – instead clinical equivalency was assumed in the economic model.

The population for which NICE recommendation is sought was a subgroup of the overall trial data. Relevant subgroup data were not available for competitor trials. Therefore, the MAIC analysis comparing benralizumab and mepolizumab was conducted in the full trial populations. The ERG considered that this added uncertainty regarding the accuracy and applicability of the MAIC results, which contributed to the economic model. The relative efficacy of benralizumab and mepolizumab between the more severe sub-group and the all-comers trial population was assumed to be equivalent. The ERG considered these assumptions to be fundamentally problematic in light of mechanism of action differences and the uncertainty this generates. These issues may impact upon the reliability of clinical inputs to the model.

1.4 Summary of cost-effectiveness evidence submitted by the company

In order to assess the cost-effectiveness of add-on benralizumab treatment, the company created a de novo economic model, based on a Markov structure. The structure is an adaptation of the model used in the previous NICE STA for reslizumab, with the added assumption that uncontrolled asthma and a moderate exacerbation can be regarded as equivalent. Add-on benralizumab was compared against standard care treatment (SOC), as well as two other add-on biologic treatments – mepolizumab and reslizumab.

The four health states used in the model were: controlled asthma, uncontrolled asthma (differentiated by an ACQ score of <1.5 vs. ≥1.5 as observed in the pivotal trials), exacerbation from a controlled state, and exacerbation from an uncontrolled state. After leaving an exacerbation state, patients can return to a controlled or uncontrolled state. Mortality was calculated as a combination of all-cause mortality and asthma-related mortality. Asthma-related mortality is only possible from an exacerbation state.

The model used a 2-week cycle length, based on trial data. A lifetime horizon was used, and costs and QALYs were both discounted at a rate of 3.5%. A response assessment is undertaken at 52 weeks, after which non-responders are assigned to SOC only. A fixed risk of add-on treatment discontinuation of 0.48% per cycle was applied to model transitions.

The model adopts the perspective of the NHS and personal social services in order to calculate costs. An event-based approach is adopted for resource costing of acute events.

Health state utilities used in the model are generated from mapped EQ-5D-5L scores (for non-OCS users), and mapped AQLQ(S)+12 scores (for OCS users). Additionally, the model incorporated disutilities from mOCS use, based on 10 different steroid-related adverse events.

The comparison between benralizumab and SOC was based on a population of severe uncontrolled eosinophilic asthma that results in a blood eosinophil count of ≥300 cells per µl, AND either ≥3 prior exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with maintenance OCS over the previous 6 months. Clinical effectiveness and health-related quality of life data was sourced from the pooled SIROCCO/CALIMA trials and the ZONDA trial.

Systematic literature reviews were conducted in order to identify sources of information for costs and utilities.

The resulting ICER was £34,284 per QALY gained, based on a PAS discounted price for benralizumab and list prices for the comparators.

The comparisons between benralizumab and the two other add-on treatments were based on the populations defined in the NICE health technology appraisals for mepolizumab and reslizumab respectively. The mepolizumab patient population was defined as: a blood eosinophil count of ≥300 cells/µl in the previous 12 months, AND either 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months OR continuous OCS use of at least the equivalent of prednisolone 5 mg per day over the previous 6 months. The reslizumab patient population was defined as: a blood eosinophil count of ≥400 cells/µl, AND 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months.

Add-on benralizumab was found to dominate both mepolizumab (less costly, more effective) and reslizumab (less costly, equally effective). However, this is based on using a discounted PAS price for benralizumab with list prices for mepolizumab and benralizumab.

A scenario analysis varied potential levels of PAS discount for the comparators by 10% increments. Based on this analysis, the ICER for benralizumab vs. mepolizumab would exceed the NICE threshold of £20,000 - £30,000 at a 50% PAS discount (or greater). Reslizumab would dominate benralizumab at a 60% PAS discount (or greater).

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

AstraZeneca considered SOC as the most important comparator in this appraisal. However, based on advice from our clinical expert, David Halpin, patients currently receiving SOC would be only those who do not need anti-IL5 therapy; about 90% of anti-IL5 therapy requiring patients would receive mepolizumab; and only a minority (up to 5%) would receive reslizumab, principally because of the intravenous route of administration. A small percentage of patients needing anti-IL5 therapy may continue on SOC for logistical reasons or personal choice. These percentages are likely to be the same in the next two years because of the issue of giving reslizumab intravenously. Therefore, the ERG consider *mepolizumab as the key comparator* in this appraisal.

We are satisfied with most aspects of the economic model proposed by the company. However, there are a number of caveats related to the company's analysis discussed below.

1.5.1 Decision analytic model

The model structure in the CS is generally appropriate for the economic evaluation and consistent with the asthma clinical pathway. It differs from those used in the mepolizumab, omalizumab, and reslizumab appraisals. The company described the model structure as being based on the model in the reslizumab STA. The main difference is in the representation of asthma-related exacerbations.

1.5.2 Asthma-related mortality

In previous economic evaluations relevant to this appraisal (i.e. of mepolizumab, reslizumab, and omalizumab), asthma-related mortality was identified as one of the key drivers of the cost-effectiveness of the treatments. It is also an important parameter in this appraisal.

AstraZeneca assumed in the main analysis that patients may die of asthma as well as of other causes, therefore both asthma-induced and all-cause mortality were incorporated into the model. All-cause mortality rates were not adjusted for asthma-related mortality because, as stated in the CS, *its impact on all-cause mortality is negligible* (Table 101, company's submission). However, overall mortality predicted by the company's model in the population of interest was about *1.5 times higher* compared to all-cause mortality in the UK general population. Therefore, the ERG consider that mortality in asthma patients was substantially overestimated.

Asthma-related mortality rates were obtained from several sources including Watson et al. (2007) [1] and Roberts et al. (2013) [2] reporting asthma deaths for 2000-2005 and 1981-2009, respectively; and the National Review of Asthma Deaths (NRAD) report (2014) [3].

According to the NRAD report, asthma deaths *decreased substantially* during 1979-2011 in all age categories except those 75 years of age and older (Figure 22); the number of deaths in this age group changed during this period rather irregularly. The ERG believe that the model assumptions should have been based on recent sources reflecting current clinical practice.

A weighted average of the probabilities of asthma death in hospital settings, used in the company's base case, was ~2.5 higher than an estimate obtained by the ERG, which was based on the BTS adult asthma audit report (2016) [4], the most recent study of the British Thoracic Society on asthma-related deaths in the UK.

In the NRAD report which was used by AstraZeneca to parameterise asthma mortality risk in hospital settings, it is stated that the majority of people (57%) who died from asthma between February 2012 and January 2013, "*were not recorded as being under specialist supervision during 12 months prior to death*". However, the patient population considered in this appraisal are patients with severe asthma *who have been on asthma treatment during the previous 12 months*. Our clinical expert confirmed that deaths due to asthma *in people who are concordant with appropriate therapy* are relatively uncommon.

We therefore believe that the mortality in the patient population relevant to this appraisal should be lower than the company's estimates.

The estimates obtained by the ERG from the BTS adult asthma audit report (2016) [4] were used in the additional analysis; this constituted *Item 1* of the ERG's base case (Section 5.3.1). In this analysis, only the probabilities of asthma-related death in hospitalised patients from 45-54 and 55-64 age categories were reduced by factor of 2.5 (see Table 60). The probabilities of asthma death in patients 45 years of age and older requiring OCS burst or Emergency room visit, and hospitalised patients of ≥65 years of age were kept unchanged as it was not possible to conduct extensive searches for relevant evidence sources due to time constraints.

When the updated probabilities were used in the company's model, the ICER for the comparison versus SOC increased by more than £2,000. The ERG believe, however, that the coarse age grouping considered by the company when modelling asthma-related mortality (i.e. 45-100 for mortality during exacerbations requiring OCS burst or ER visit, and 65-100 for mortality in hospitalised patients) may have biased the results in favour of benralizumab. The ICER would have increased even further if mortality in older patients was modelled using narrower age categories.

When asthma-related mortality was set to zero in a company's scenario analysis, the ICER for benralizumab vs. SOC increased from £34,284 to £67,260 per QALY gained.

1.5.3 Patient's age at baseline

Age at treatment initiation is an important driver of the cost-effectiveness of benralizumab due to the assumption of age-dependent risk of mortality in asthma patients.

The average age of patients at treatment initiation in the company's analysis was ~50 years (based on pooled SIROCCO/CALIMA data), which the ERG consider as not accurately reflecting UK clinical practice. According to advice from the clinical expert, Prof Halpin, adult people with severe asthma are often younger. The average age of UK adult patients with difficult asthma from a UK registry, reported by Heaney et al. (2010) [5], was 44.9 years.

In the base case, the ERG adopted the company's assumption of the mean patients' age of 50 years at the start of treatment *for consistency with the clinical effectiveness data* from the pivotal trials (Section 5.2.5.2.3). A scenario analysis was conducted assuming the mean age of 44.9 years reported by Heaney et al. (2010) [5] (Section 5.3.2.3). Under this assumption, the base-case cost-effectiveness results changed only slightly. However, under a PAS price for mepolisumab, this assumption had a moderate effect on the cost-effectiveness of BEN vs. MEPO.

1.5.4 Proportions of patients on mOCS at baseline

In the company's model, 54.1% and 78.6% of patients in BEN vs. SOC and BEN vs. MEPO, respectively, were on mOCS treatment at baseline (Section 5.2.3.2.4). The ERG believe that these proportions were overestimated and not reflective of clinical practice.

The ERG noted (p. 164, company's submission): "In order to calculate the percentage of patients in each population who would be dependent on mOCS at baseline in UK clinical practice, an analysis of the Kerkhof 2017 paper, a UK observational research study, was undertaken. For a full description of the baseline characteristics refer to Table 22". However, the proportions reported by Kerkhof - 16.5% in patients 18-64 y.o. and 17.1% in patients >=65 y.o. - were substantially lower than those in the company's base case. Also, as shown in Table 22 (company's submission) which the company referred to, *only about 23% of patients in pooled SIROCCO/CALIMA* dataset were on mOCS at baseline.

Of note, in BEN vs. RESLI comparison, it was assumed that no patients take mOCS in line with the population defined in the NICE guidance on reslizumab.

In the main analysis, the ERG used the estimate of 41.7% obtained from a UK registry of patients with difficult to control asthma (Heaney et al., 2010 [5]). This assumption constituted *Item 2* of the ERG's base case (Section 5.3.1).

When this rate was applied for the BEN vs. SOC comparison in the company's model, the ICER increased to £36,546 per QALY gained. This assumption had no effect on the

qualitative result for the BEN vs. MEPO comparison in the company's base case, i.e. BEN stayed dominant. Under the PAS price for MEPO, however, the lower rate of mOCS use at baseline led to a substantial increase in the ICER.

An estimate reported in Kerkhof et al. (2017) [6], 17%, was assumed in a scenario analysis conducted by the ERG (Section 5.3.2.3).

1.5.5 Administration costs of biologics

Administration costs for benralizumab, mepolizumab and reslizumab were underestimated since additional nurse time required to monitor for anaphylaxis after administration of the biologics was not considered in the company's analysis (Table 66, Section 5.2.8.3).

The company assumed that the administration of benralizumab would take less time than the administration of mepolizumab as there is no need for reconstitution. Based on clinical advice, however, the reconstitution time for mepolizumab is likely to add a negligible amount of time to overall administration, since it is done during routine nurse interaction with patient. Therefore, the ERG assumed *no difference in the administration time for BEN and MEPO*. Of note, both drugs are administered subcutaneously.

In the ERG's base case, administration costs for BEN and MEPO were adopted from mepolizumab appraisal [7]. Drug administration was costed at £44.64 for the first 3 doses, and £17.86 from dose 4 onward, taking into consideration monitoring time for anaphylaxis during *the first 3* administrations (see Table 66 for further details). Importantly, in the mepolizumab appraisal it was assumed that monitoring for anaphylaxis is performed up to week 16. In the ERG's base case, however, it was assumed, based on clinical advice, that monitoring is required during the first 3 administrations only.

For reslizumab, in addition to monitoring cost, a day-case admission for the first three administrations was assumed in addition to cannula insertion as in the updated analysis for reslizumab appraisal.

The updated costs constituted *Item 3* of the ERG's base case (Section 5.3.1).

When these assumptions were incorporated into the AstraZeneca model, the ICER for BEN vs. SOC increased by ~£400. As for comparisons with the biologics, these assumptions were less favorable for BEN but did not change the results qualitatively, i.e. BEN remained dominant.

Two scenario analyses were carried out by the ERG: one assuming that monitoring is conducted *up to 16 weeks* from treatment initiation (as in the mepolizumab appraisal [7]), and the other SA assuming that monitoring is required for the *whole treatment period* (Section 5.3.2.3).

1.5.6 Acquisition cost of reslizumab

The exact dosing of reslizumab depends on a patient's bodyweight. Reslizumab is available as a 2.5ml or 10ml vial (25mg and 100mg). In the CS, reslizumab dosing and wastage were based on a mean patient weight of 75.2 kg, as published in the reslizumab NICE STA TA479 [8].

The ERG consider this inappropriate. Firstly, the mean weight of adult patients in the ZONDA trial was 83.1 kg (Table 54), and our clinical expert confirmed that the subgroup of patients with severe asthma have a high body mass index (BMI). Secondly, the acquisition cost should have been estimated from a weight distribution of severe asthma patients, and a vial dosing scheme from the summary of product characteristics (SmPC) for reslizumab [9].

This strategy was employed by the ERG in all additional analyses. We estimated reslizumab dosing and wastage using a weight distribution of people with severe asthma reported in Haselkorn et al. (2009) [10] (5.2.8.1.3). This assumption constituted *Item 4* of the ERG's base case (Section 5.3.1).

Incorporation of the weight distribution and the vial-based dosing scheme into the company's model improved the cost-effectiveness of benralizumab.

1.5.7 Treatment discontinuation rate

As the ERG noted in the reslizumab and mepolizumab Final Appraisal Determinations (FADs), treatment stopping rules for these treatments should be implemented at 12 months after the start of treatment, and treatment response should be reassessed each year.

In the AstraZeneca model, treatment response was evaluated 52 weeks after treatment initiation but it was not reassessed on an annual basis. In addition to treatment discontinuation at 52 weeks, the company implemented treatment attrition via a risk of treatment discontinuation applied to each model cycle in every health state. The company stated that the treatment attrition rate of 11.8% per year, assumed in the company's base case, was derived from the pivotal trials. The ERG believe that this rate was slightly overestimated (see Table 52).

In the ERG's base case, an annual attrition rate of 10.2% (the average rate in the pivotal trials) was used; this constituted *Item 5* of the ERG's base case (Section 5.3.1).

This change had virtually no effect on the company's base-case results. Under the PAS discount for MEPO, however, the decrease in the attrition rate moderately increased the relevant ICER.

Of note, in the MEPO appraisal, the annual attrition rate was 10%.

The ERG believe that it would not be unreasonable to assume that some patients would return to treatment after discontinuation. As such, the overall discontinuation rate may be lower.

1.5.8 Utilities

1.5.8.1 Health state utilities

Health-state utilities used in the company's model were obtained from two different measures: the EQ-5D-5L, and AQLQ(S)+12 (an asthma-specific quality of life measure). Both measures were collected in the SIROCCO and CALIMA trials, whilst only the AQLQ(S)+12 was collected in ZONDA [11-13]. Both measures were mapped onto EQ-5D-3L and used in the company's base-case analysis.

The ERG consider the approach undertaken by AstraZeneca appropriate as the evidence came from the pivotal trials. The ERG requested IPD to verify the utility values used in the model. The requested data, however, was not provided by AstraZeneca (see the company's response in Section 5.2.6.1). Therefore, the health state utility values used in the company's model could not be verified by the ERG.

According to a NICE position statement on use of ED-5D-5L valuation set, the EQ-5D-3L should be used in the reference case for HTA submission. The ERG is aware that 3L and 5L systems can produce substantially different estimates of cost-effectiveness, and incremental QALYs based on 3L version of EQ-5D are usually higher than those estimated from 5L (Fig 3, Hernandez Alava et al. (2018) [14]). The ERG carried out a scenario analysis using utilities based on EQ-5D-5L from pooled SIROCCO/CALIMA dataset (this scenario analysis was also conducted by AstraZeneca). Of note, this only affects the non mOCS patients in the model as this measure was collected in the SIROCCO and CALIMA trials only, the evidence base for modelling non mOCS patients.

Age and gender adjustment of health-state utility values

According to the NICE guidance (DSU TSD 12) [15], health state utility values should be adjusted for the effects of age and gender to take into consideration the natural decline in quality of life associated with co-morbidities. In the appraisal of mepolizumab, committee considered that utilities should be age-adjusted, and this adjustment was incorporated in the updated base case (p. 73, committee papers dated 1 December, 2016).

The company, however, did not consider such an adjustment which overestimated the benefits of treatment over patient lifetime. Due to time constraints, the ERG did not perform this adjustment.

1.5.8.2 Disutilities of asthma exacerbations

The duration of exacerbations assumed in the company's model, was based on an analysis by Golam et al. (2017) which was *previously* conducted by AstraZeneca. This was a post-hoc analysis of pooled data from SIROCCO and CALIMA. Based on this source, it was assumed that exacerbations impact a patient's quality of life over an *8 weeks* period including time prior to the start of exacerbation and time post exacerbation. The estimate was based on *a visual inspection* of a graph showing mean weekly utilities observed in pooled SIROCCO and CALIMA data. The ERG believe, however, that the duration of disutility applied in the company's model for each type of exacerbation was substantially overestimated. For example, the loss in utility due to hospitalisation (which was assumed to last 8 weeks) is not consistent with the BTS adult asthma audit report (2016) [4], where the mean length of asthma-related hospital stay was 3 days in the UK in 2016, "with a significant number of patients discharged within 24 hours".

As was discussed in the MEPO appraisal, the duration of utility decrement in the MENSA trial was 13 days for OCS burst, 10 days for ED visit, and 21 days for hospitalisation [7]. This was a preferred assumption of the Appraisal Committee for that appraisal. In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) [16]. In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely *less than the model cycle of 4 weeks*.

Therefore, the ERG believe that durations of disutilities substantially shorter than those assumed by the company would be more plausible.

1.5.9 Health state costs

The ERG found some inconsistencies and/or inadequately explained calculations for health state costs. Upon replication of the analysis with the latest PSSRU cost data, the health state cost for an "Exacerbation" state was found to be moderately lower than that in the CS, while the other health state costs were similar to those from the CS. The updated costs, however, had a very small impact on the cost-effectiveness results: the base-case ICER for BEN vs. SOC increased by ~£200, while the results for the other comparisons did not change qualitatively, i.e. BEN stayed dominant (Section 5.2.8.4). Therefore, the ERG adopted the health state costs used in the company's analysis.

1.6 ERG's commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company provided clinical effectiveness results of relevant trials for the population in line with the licensed indication involving adult patients with baseline blood eosinophil count of ≥ 300 per μL and on high dose ICS/LABA with or without OCS.

The ERG believe the analysis of the key pivotal trials, SIROCCO, CALIMA and ZONDA, to be adequate and that the pooling of the subgroups from the CALIMA and SIROCCO trials was appropriate.

The ERG consider the MAIC analysis to be largely conducted in line with NICE DSU recommendations.

Benralizumab appeared to be well tolerated with an adequate safety profile in the short term (up to one year). The most common reported side effects included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache and bronchitis, although these occurred at similar rates compared to placebo.

The ERG identified several minor errors in the company's cost effectiveness model. However, no individual correction (nor the application of all corrections simultaneously) affected ICERs by any significant amount.

1.6.2 Weaknesses and areas of uncertainty

1.6.2.1 Clinical effectiveness

Data in these main analyses included also patients with two baseline exacerbations in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations) the year preceding trial enrolment.

The prognosis of the ZONDA population may differ from the prognosis of the pooled SIROCCO/CALIMA population.

The company noted that reductions in exacerbation rates were observed to be greater in the SIROCCO than in the CALIMA trial and suggested that the observation might be due to three key drivers: regional effect, exacerbation history, and background medication. The ERG consider it likely that the difference in magnitude of treatment effect is related to unknown confounders.

The ERG had some concerns about the methodology of the MAIC analysis. There was evidence of selective outcome reporting, whereby outcomes for which benralizumab had unfavourable results in the CSR were not reported in the CS or considered as clinical inputs

to the economic model. The effect modifier selection process for the MAIC analysis excluded effect modifiers that were not in imbalance between the benralizumab and mepolizumab trials contrary to NICE DSU recommendations. Data were imputed from one technology to another despite benralizumab having a fundamentally different mechanism of action from mepolizumab and reslizumab. No clinical analysis was conducted to compare benralizumab and reslizumab – instead clinical equivalency was assumed. The relative efficacy of benralizumab and mepolizumab between the more severe sub-group and the all-comers trial population was assumed to be equivalent. Neither of these assumptions was evidence based.

AstraZeneca declined the ERG's request to provide IPD within the time frame of the appraisal, precluding the ERG from checking the clinical MAIC analysis which incorporated a considerable amount of unpublished data.

While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted]

The CS states that one patient in the benralizumab arm died due to AEs, which was not considered to be study drug-related. However, the ERG noted that the ZONDA CSR [redacted]

The ERG noted that the safety profile obtained from the CS pivotal RCTs was based on trial data for patients concurrently treated with oral corticosteroids. The ERG noted that the CS did not look to include observational studies assessing safety of benralizumab.

While no cases of anaphylaxis were observed in SIROCCO or CALIMA, the ERG noted that patients were excluded from SIROCCO and CALIMA trials if they had a history of anaphylaxis with any biologic drug. It has been reported in the literature that anaphylaxis may occur rarely (0.3%) after exposure to reslizumab and the ERG suggest further studies are needed to establish risk of anaphylaxis for benralizumab for people with no prior exposure to any biologic drug.

The ERG noted the absence of trial data to establish the risks of benralizumab on malignancy and safety in the medium to long term as well as during pregnancy.

1.6.2.2 Cost effectiveness

The ERG had concerns regarding the continuation criteria for treatment with benralizumab which were not specified in the CS, and therefore could not be critiqued by the ERG.

However, this is an important driver of the ICER for the comparisons of BEN versus MEPO (see a confidential appendix).

The ERG could not verify assumptions on treatment effectiveness and health-related quality of life in the company's model (health state transition probabilities and utilities in particular) since individual patient data requested by the ERG were not provided by the company (see the company's response in Section 5.2.6.1). The ERG, however, believe that the health state transition probabilities used in the company's analysis could not be robust given the relatively small samples on which those estimates were based.

Health-state utilities used in the company's model were obtained from two different measures: the EQ-5D-5L, and AQLQ(S)+12 (an asthma-specific quality of life measure). Both measures were collected in the SIROCCO and CALIMA trials, whilst only the AQLQ(S)+12 was collected in ZONDA [11-13]. These trials, however, were not powered to assess differences in health-related quality of life. Therefore, the analysis should be viewed with caution.

Clinical inputs and health-related quality of life outcomes were assumed as identical between benralizumab and reslizumab. This is because the company determined that a MAIC could not be conducted between the two treatments, due to significant differences between the relevant trials (see Section 4.4). The ERG believe that identical effectiveness of these drugs is unlikely in practice due to differences in their mechanisms of action, and therefore the cost-effectiveness results for the comparison of benralizumab vs. reslizumab should be considered with caution. However, the ERG adopted the same-effectiveness assumption for BEN and RESLI as in the company's submission since no alternative estimate of the relative effectiveness of BEN vs. RESLI was available.

The ERG believe that hospitalisation rates were overestimated in the CS since about 1/3 of all patients in the pivotal trials were from Eastern Europe, where the asthma-related hospitalisation rate was substantially higher than in Western European countries, 42% vs. 18%, respectively (Table 59). The ERG believe that, from this perspective, the trial populations were not representative of the UK patient population. The ERG noted that hospitalisation rates contribute substantially to the cost of treating exacerbations, and therefore, higher hospitalisation rates are favourable to benralizumab.

AstraZeneca assumed no waning effect of treatment in the base case, and no scenario analysis exploring the alternative assumption was conducted by the company. AstraZeneca stated: "given that there is no evidence to suggest that there is a loss of efficacy and that previous appraisals in this area have also not included this effect and we believe this approach is justified" (p.300, CS). However, according to the Guide to the Methods of Technology Appraisal [17], additional analyses "assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions" should be conducted. The Appraisal Committee for mepolizumab appraisal considered that a scenario analysis exploring a waning effect would be valuable (p. 100, committee papers dated 8 June, 2016 [7]). Such scenario analyses were conducted by ScHARR, the ERG for the mepolizumab appraisal. They predicted substantially higher ICERs compared to those assuming no waning effect. Therefore, the ERG believe that a further analysis with respect to this assumption would be appropriate.

AstraZeneca conducted MAIC scenario analyses which included the MUSCA trial. In those scenarios, after matching,

[redacted]

[redacted] (Section 4.4.8). The company did not examine the effect of inclusion of MUSCA on the cost effectiveness of benralizumab. The ERG noted that when the results of these analyses ([redacted]47) were incorporated into the company's model, the effect on the base-case ICER for BEN vs. MEPO was negligible. However, under the PAS discounted price for MEPO, the ICER increases *very substantially* (see the ERG's confidential appendix for further details).

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.7.1 Base-case analysis

The ERG made several changes to the company's base case assuming:

- lower probabilities of asthma-related mortality, 0.0041 per model cycle (Item 1)
- a lower percent of patients on mOCS at baseline, 41.7% (Item 2)
- drug administration costs for the biologics reflective of the NHS clinical practice (Item 3)
- reslizumab acquisition cost, with dosing and wastage based on a weight distribution and the vial-based dosing scheme for reslizumab (Item 4)

- a lower treatment discontinuation rate of 10.2% per year based on the average rate from the pivotal trials (Item 5)

The individual and combined effect of all amendments made by the ERG to the company's base case are shown in Table 1.

Table 1 Derivation of the ERG's base-case ICERs (£ per QALY)

	Item #	ERG's base case	Company's base case	ICER for BEN+SOC vs. SOC	ICER for BEN+SOC vs. MEPO + SOC	ICER for BEN+SOC vs. RESLI + SOC
1	Asthma-related mortality	Age-stratified probabilities for hospitalised patients of 65 years of age and older, and for patients of 45-100 years old requiring OCS and NR the probabilities are the same as in the CS; in all other age categories, they were assumed ~2.5 times lower than in the company's model.	See Table 60	£36,398	BEN dominates	BEN dominates
2	mOCS use at baseline	41.7% (Heaney et al., 2010) for all treatments	54.1% for SOC comparison, 78.6% for the MEPO comparison	£36,531	BEN dominates	NA
3	Administration costs of biologics	Costed supervision after the admin of biologics; assumed the same admin time for MEPO and BEN; assumed admin cost for RESLI as in the RESLI appraisal.	Monitoring time not costed; administration of MEPO takes 5 mins longer than for BEN; 55 mins for RESLI	£34,646	BEN dominates	BEN dominates
4	Acquisition cost for RESLI	Based on a bodyweight distribution from Haselkorn et al., (2009) [10] and the vial-based dosing scheme from SmPC for RESLI [9]	75.2kg	NA	NA	BEN dominates
5	Treatment discontinuation rate	0.0041/cycle (average across the pivotal trials)	0.0048/cycle	£34,346	BEN dominates	BEN dominates

Item #	ERG's base case	Company's base case	ICER for BEN+SOC vs. SOC	ICER for BEN+SOC vs. MEPO + SOC	ICER for BEN+SOC vs. RESLI + SOC
ERG's base case: 1+2+3+4+5			**£39,135**	**BEN dominates**	**BEN dominates**
Company's base case:			**£34,270**	**BEN dominates**	**BEN dominates**

Note: Comparison between benralizumab and reslizumab assumes equal effectiveness (i.e. only costs differ).
NA, not applicable

As shown in Table 1, the cost-effectiveness of add-on benralizumab (+PAS) compared with SOC alone is £39,135 per QALY gained in the Base Case Population. Benralizumab provides an additional [redacted] QALYs at an additional cost of £[redacted] (see Table 75).

Add-on benralizumab is dominant versus add-on mepolizumab with QALY gains of [redacted] and cost savings of £[redacted] in the mepolizumab NICE recommended population (Table 76).

Add-on benralizumab is less costly versus add-on reslizumab, with cost savings of £[redacted] in the reslizumab NICE recommended population (Table 77).

Results most relevant to the NHS, i.e. those based on the PAS prices of all biologics, are presented in the confidential appendix.

1.7.2 Sensitivity analyses

The ERG carried out additional deterministic, probabilistic and scenario analyses for the preferred base case. Scenario analyses conducted by the ERG are reported in Table 2 together with ERG's preferred base-case results.

Table 2 Scenario analyses relative to the ERG's base case (list prices for comparators)

Assumptions	ICER for BEN vs. SOC	ICER for BEN vs. MEPO	ICER for BEN vs. RESLI
Set asthma-related mortality to zero	£73,560	BEN dominates	BEN dominates
mOCS use at baseline of 17% (as in Kerkhof et al. 2017) [6]	£44,425	BEN dominates	BEN dominates
Administration costs of biologics assuming monitoring for the entire treatment duration	£40,089	BEN dominates	BEN dominates
Use EQ-5D-5L utilities from the pivotal trials directly, rather than mapped values onto EQ-5D-3L	£40,066	BEN dominates	BEN dominates

Assumptions	ICER for BEN vs.		
	SOC	**MEPO**	**RESLI**
Administration costs of biologics assuming monitoring for the first 16 weeks (benralizumab and mepolizumab)	£39,161	BEN dominates	BEN dominates
PenTAG Base Case	**£39,135**	**BEN dominates**	**BEN dominates**
Patient's age at the start of treatment set to 44.9 (as in Heaney et al. (2010) [5])	£38,340	BEN dominates	BEN dominates
Method of calculating acquisition cost of reslizumab as in the CS (RESLI comparison)	NA	NA	BEN dominates
Using results of MAIC scenario analysis for exacerbation trials including MUSCA trial (MEPO comparison)	NA	BEN dominates	NA
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	£38,246	BEN dominates	BEN dominates

Note: Comparison between benralizumab and reslizumab assumes equal effectiveness (i.e. only costs differ).

In all scenario analyses, ICERs for the comparison against SOC were well above the threshold of £30,000 per QALY. The highest ICER, £73,560 per QALY gained, was predicted when asthma-related mortality was set to zero. Using EQ-5D-5L utilities from the pivotal trials resulted in an ICER greater than £40,000 per QALY. A similar result was obtained when monitoring time for anaphylaxis for the entire treatment duration was modelled. Assuming monitoring for the first 16 weeks only had virtually no effect on the ERG's base-case ICER for this comparison.

For the comparisons against mepolizumab and reslizumab, in all scenario analyses, the results were qualitatively the same as in the company's and ERG's base cases, i.e. benralizumab was dominant.

See Section 5.3.2 for further details on sensitivity analyses carried out by the ERG.

2 Background

2.1 Critique of company's description of underlying health problem

Asthma is a multifactorial and often chronic respiratory illness. People with severe uncontrolled asthma make a relatively small proportion of the population of adults with asthma, up to 10% as reported by Chung (2014) [18]. Their care, however, is estimated to account for more than 60% of the costs associated with asthma, which are primarily for medications [19]. Severe asthma also imposes a substantial burden owing to symptoms, exacerbations, and medication side effects, which have profound consequences for mental and emotional health, relationships, and careers.

There is no universally accepted definition of difficult (or uncontrolled) asthma. However, it is reasonable to consider it present when people have persistent symptoms and frequent exacerbations, despite being treated at steps 4 or 5 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines [20]. Such patients typically receive high dose inhaled steroids (>= 800 mg beclomethasone equivalent), a long acting betta$_2$ agonist, plus add-on treatment.

Eosinophilic asthma is a phenotype of asthma characterized by the higher than normal presence of eosinophils in the lung and sputum. It has been shown that the numbers of eosinophils in the blood and bronchial fluid correlate with asthma severity. As reported by Kerkhof et al. (2017) [6], less than 1% of patients in the UK general population have uncontrolled *eosinophilic* asthma.

Interleukin-5 (IL-5) plays a fundamental role in eosinophilic differentiation, maturation, activation and inhibition of apoptosis [21]. Monoclonal antibodies targeting IL-5 or its receptor (IL-5R) have been developed, with recent studies suggesting that they reduce asthma exacerbations, improve health-related quality of life and lung function. Benralizumab, mepolizumab and reslizumab are "anti-IL-5" treatments considered in this appraisal: add-on treatment with benralizumab is compared to standard of care (SOC) alone, and the two other biological add-ons, mepolizumab and reslizumab.

As an anti-eosinophil humanised, monoclonal antibody, benralizumab specifically binds to the human IL-5 receptor alpha subunit (IL-5Rα), with a unique mode of action. By binding to eosinophils through IL-5Rα, benralizumab blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil. Additionally, due to an afucosylated section on the molecule itself, benralizumab increases the affinity of eosinophils to Natural Killer (NK) cells. This leads to a rapid and near complete depletion of eosinophils and basophils through enhanced antibody-dependent cell-mediated

cytotoxicity (ADCC), resulting in a systemic efficacy response [22]. Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84 [22].

In contrast, mepolizumab and reslizumab act by binding to IL-5 and inhibiting IL-5 signalling, thereby indirectly reducing the activation, proliferation, and survival of eosinophils – this ultimately results in eosinophil reduction but not depletion.

2.2 Critique of company's overview of current service provision

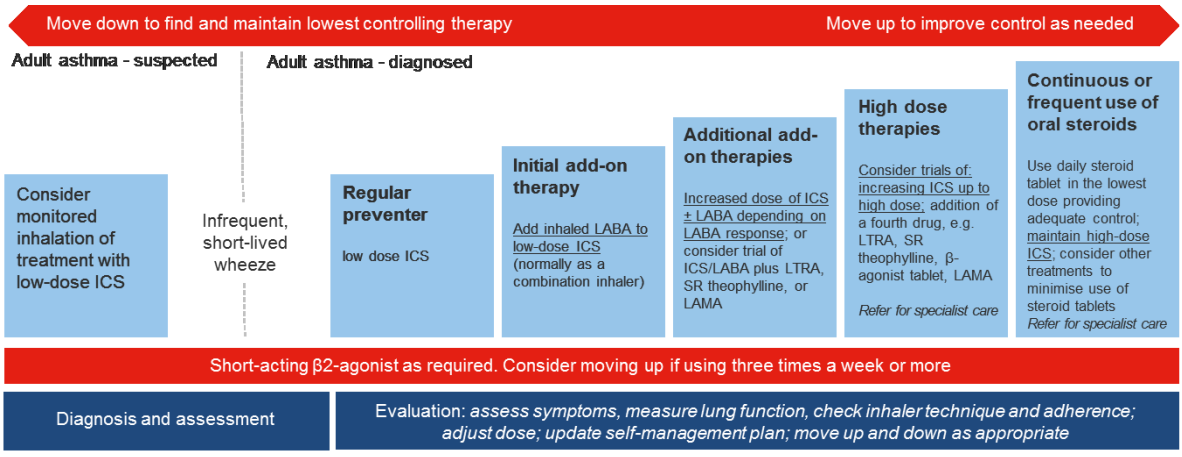
In the UK, the most commonly used treatment guidelines are those from BTS/SIGN and those recently published by NICE. The aim of asthma management is control of the disease. In BTS/SIGN guidelines, complete control of asthma is defined as [23]:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV_1 and/or PEF>80% predicted or best)
- minimal side effects from medication.

For people with severe asthma, many of these goals will be unachievable, and priorities may surround relative rather than complete improvements for these outcomes [24].

Key principles of pharmacological management for asthma, as described by BTS/SIGN, are presented in Figure 2 [23].

Figure 2 BTS/SIGN guidelines for the management of asthma



ICS = inhaled corticosteroid; LABA = long acting beta agonist; LTRA = leukotriene receptor antagonist; LAMA = long acting muscarinic receptor antagonist

Source: BTS/SIGN. British Guideline on the Management of Asthma. 2016 [23]

A stepwise approach to treatment is recommended, moving up to improve control as needed, and moving down to find and maintain the lowest controlling therapy.

ICS are the recommended preventer drug for adults and children, for achieving overall treatment goals. LABAs are the first choice for add-on therapy to ICS in adults, and should be considered before increasing the dose of ICS. If asthma control remains suboptimal after the addition of a LABA, more intense treatment should be considered following a reassessment of diagnosis, adherence, and inhaler technique. For patients who demonstrate an improvement when a LABA is added but for whom control remains inadequate, options include increasing the ICS dose, or adding on a LTRA, LAMA, or theophylline. For patients who do not demonstrate an improvement when a LABA is added, the LABA should be stopped and an increased dose of ICS, an LTRA, or a LAMA (off-label) should be added.

For patients who are inadequately controlled on a combination of SABA, medium-dose ICS, and an additional drug (usually a LABA), there are limited options. BTS/SIGN states that the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit in inadequately controlled adults, although results are currently inconclusive. Other options include stepping up ICS to a high dose (adults) or medium dose (children), or adding an LTRA, theophylline, or slow-release β2 agonist. BTS/SIGN does not indicate a preference for either of these options based on the available evidence, although it is acknowledged that the potential for side effects is greater with theophyllines and β2 agonist tablets.

The recently updated NICE guidance on asthma management also recommends a stepwise approach, but with some differences in the sequence of treatment options (such as earlier positioning of ICS/LTRA, and a preference for a maintenance and reliever regimen over SABA for reliever therapy if uncontrolled on low-dose ICS/LABA) [25].

For those patients who remain inadequately controlled despite stepping up to high dose therapies, the recommended treatment option is daily OCS (prednisolone), at the lowest dose providing adequate control. Patients requiring OCS should generally be referred to specialist care, and monitored for OCS-induced side effects, such as elevated blood pressure, diabetes, decreased bone mineral density (BMD), cataracts, and glaucoma.

Alternatives to OCS are severely limited, but include the biologic treatments mepolizumab and omalizumab.

NICE recommended mepolizumab [7] as an add-on to optimised standard therapy as an option for treating severe refractory eosinophilic asthma in adults, only if:

- *the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and*
- *the person has agreed to and followed the optimised standard treatment plan and*
    - *has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or*
    - *has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months"*

Reslizumab is recommended [8] as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:

- *the blood eosinophil count has been recorded as 400 cells per microlitre or more*
- *the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months"*

Omalizumab is recommended [26] as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy 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), and*
- *only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.*

Omalizumab, however, was not considered in the Final Scope for this appraisal.

The ERG believe that the company's overview of current service provision was appropriate and relevant to the decision problem under consideration.

3 Critique of company's definition of decision problem

3.1 Population

Based on clinical advice, the target population - patients with ≥3 exacerbations needing systemic corticosteroids in previous year, or mOCS over previous 6 months - was considered appropriate and to be representative of UK clinical practice in England. The final NICE scope restricts the population to adults (≥18 years), whilst the pivotal trials of benralizumab included patients ≥12 years. However, the ERG noted that the majority of included patients were ≥18 years. The company provided clinical effectiveness results of relevant trials for the population in line with the licensed indication involving adult patients with baseline blood eosinophil count of ≥ 300 per µl and on high dose ICS/LABA with or without OCS. The company also indicated the patient subgroup for which a NICE recommendation is sought; patients with blood eosinophil count ≥ 300 per µL and either 1) ≥ 3 exacerbations needing systemic corticosteroids in the past 12 months, or 2) ≥ 6 months previous treatment with OCS.

The ERG agreed that the model populations for the comparisons between BEN vs. MEPO, and BEN vs. RESLI should be in line with the patient populations in the respective NICE guidances for MEPO and RESLI.

3.2 Intervention

Benralizumab is indicated as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA. The intervention considered in the company's submission matches the one defined in the NICE scope.

3.3 Comparators

The comparators considered in the CS match those in the scope. AstraZeneca considered SOC as the most important comparator in this appraisal. The ERG, however, believe MEPO to be the major comparator in this STA. Based on clinical advice, patients currently receiving SOC would be those who do not need anti-IL5 therapy, < 5% of all patients. About 90% of patients requiring anti-IL5 therapy would receive mepolizumab, and only a minority (up to 5%) would receive reslizumab because of the intravenous route of administration. These percentages are likely to be the same in the next 2 years because of the issue of giving reslizumab intravenously.

3.4 Outcomes

Outcome measures of the clinical effectiveness evidence are broadly in line with the NICE scope. Time to discontinuation was listed in the final NICE scope but was not reported in the CS, although withdrawals were reported.

The outcomes of the economic analysis are in line with the scope except the following:

- Patient evaluation of response was not available in the trial data
- Discontinuation was treated as a constant rather than a time dependent variable as is consistent with other appraisals in severe asthma.

3.5 Other relevant factors

There were no equity considerations in this appraisal. Both mepolizumab and reslizumab have patient access schemes (PASs) agreed with the Department of Health. Since the PASs are confidential, base-case ICERs were calculated using the net price of benralizumab and the list prices of mepolizumab and reslizumab.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

The CS included a systematic review of benralizumab RCTs to provide data relating to the clinical effectiveness and safety of benralizumab and for the match adjusted indirect comparison of benralizumab versus mepolizumab. In addition, one of the RCTs provided data on reduction of oral glucocorticoids with benralizumab.

4.1.1 Searches

AstraZeneca presented a literature search protocol to support its review of clinical effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy, and a search of conference websites. The literature search was carried out in October 2017.

The bibliographic database searching used a search strategy that took the following form:

1. (controlled index terms for different types of asthma) OR
2. (free-text terms for asthma, lung allergy) AND
3. (various controlled index terms relating to Randomised Controlled Trials) OR
4. (various free-text terms for randomized controlled trial) AND
5. (controlled index terms for benralizumab and comparators) OR
6. (free-text terms for benralizumab, comparators and some proprietary drug names) AND
7. (a filter to limit results to human studies, not animal ones) NOT
8. (terms to exclude letters, conference reviews, editorials, notes, reviews as publication type).

The search strategy was applied in the following bibliographic databases: Medline and Embase (Elsevier at embase.com), Medline-in-Process (PubMed), and The Cochrane Library (CENTRAL only).

The following conference websites were searched: American Thoracic Society, European Respiratory Society, American College of Chest Physicians. A selection of trials registries including clinicaltrials.gov and the WHO registry were searched for relevant, unpublished studies.

The literature searching for clinical effectiveness studies was reasonably well conducted and reported. However, there were a few concerns:

- The filter used to limit to RCTs was an ‘adapted’ version of the SIGN (Scottish

Intercollegiate Guidelines Network) RCT filter. It was unclear why it was necessary to alter this validated filter, or why a validated search filter was not used to limit to RCTs.

- The proprietary drug name 'Fasenra' was not included in the search terms, although proprietary drug names for comparator drugs were included.
- The ERG did not have access to Embase.com so were unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy is debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).

Titles of included and excluded papers for the systematic review were not listed. Data extraction methods for included papers were not detailed.

4.1.2 Inclusion criteria

The inclusion criteria for the company's systematic review of effectiveness are summarised in Table 3

Table 3 Eligibility criteria (PICOs) for the systematic review

Population	• Age: adults and adolescents (≥12 years) • Gender: any • Race: any • Disease: severe asthma that is uncontrolled despite treatment with medium- to high-dose ICS plus at least one additional controller
Interventions	• Benralizumab
Comparators	• Biologics (approved and in development) • Mepolizumab • Omalizumab • Reslizumab • Placebo/best supportive care • Medium or high-dose ICS + at least one additional controller. • Medium dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 2 additional controller (e.g. LABA + LAMA/LABA+LTRA) • High-dose ICS + at least one additional controller + OCS maintenance treatment
Outcomes of interest	Efficacy and quality of life outcomes: • Pre-bronchodilator FEV_1 • Post-bronchodilator FEV_1 • Peak expiratory flow • Asthma exacerbation (overall exacerbation, exacerbations requiring systemic corticosteroids, ER visit and/or hospitalisation) • Definition of exacerbation • Number of patients with exacerbations • Total number of exacerbations experienced over the duration of the study • Mean rate of exacerbations per patient per year • Time to first exacerbation • Symptom-free days • Asthma control measured by ACQ • Asthma symptoms (overall, day-time, night-time symptom, night-time awakening)

	• Oral corticosteroids sparing efficacy • AQLQ or mini AQLQ • SGRQ • EQ-5D • WPAI	
	Safety outcomes: • Any adverse events • Any serious adverse events • Any treatment-related adverse events • Bronchitis • Cardiac events • Cough • Dry mouth	• Hoarseness or dysphonia • Mortality • Nausea • Oral candidiasis • Pneumonia • Palpitations • Sinusitis • Tremor • Upper respiratory tract infections
	Tolerability • All withdrawals • Withdrawal due to adverse events • Withdrawal due to lack of efficacy	
Study designs	• RCTs	
Language	• Database to be searched irrespective of language • English language studies were included in SLR	
Publication timeframe	• Database inception to present date (searched initially on 17th June 2016 and subsequently on 17 October 2017) • Conference proceedings for past 3 years (searched on 17 October 2017)	

Source: company submission section B.2.1 table 9, p. 63

The inclusion criteria were broadly appropriate and consistent with the decision problem specified in the final NICE scope. Studies of patients aged ≥12 years were included. The final NICE scope restricts to adults (≥18 years), whilst the pivotal trials of benralizumab included patients ≥12 years but the majority of included patients were ≥18 years.

Therefore, this inclusion criterion appeared broadly appropriate. Appropriate interventions, comparators, outcome measures and study types were included. Time to discontinuation was listed in the final NICE scope but was not reported in the CS, though withdrawals were reported in CS pp. 91 – 93.

4.1.3 Critique of data extraction

A two-stage screening process was adopted, with a first-pass screening for titles and abstracts followed by second-pass screening for full-text publications. Screening was carried out by two independent reviewers, with any discrepancies reconciled by a third independent reviewer. The ERG considered this process to be good methodological practice. Data extraction methods for included papers were not detailed in the CS and so the ERG could not critique the company's data extraction methodology.

Quality assessment

Quality assessment of RCTs was undertaken using the minimum criteria for assessment of risk of bias in RCTs as described in guidance by the Centre for Reviews Dissemination

(CRD) [27]. Quality assessment using the Jadad score was also undertaken in the CS. However, the ERG noted that the Jadad scale has received criticism for being over-simplistic and placing too much emphasis on blinding, and can show low consistency between different raters. Furthermore, it does not take into account allocation concealment, viewed by The Cochrane Collaboration as paramount to avoid bias [28]. Consequently, the ERG only critiqued the CS quality assessment using CRD criteria presented in the CS.

Evidence synthesis

For the two benralizumab trials with a primary endpoint of reduction in exacerbations (SIROCCO and CALIMA), meta-analyses were provided in the CS for some outcomes but not for others.

4.1.4 Critique of key trials

Summary of excluded studies

Two key trials for benralizumab (BISE and GREGALE) did not meet the inclusion criteria. BISE was a randomised, placebo-controlled, double-blind Phase 3 trial in patients with mild to moderate persistent asthma [29] GREGALE was a phase 3 trial that assessed the functionality, reliability, and performance of a pre-filled syringe with benralizumab administered at home, and was excluded as it was open-label and single-arm; further, the trial was not powered to assess efficacy outcomes [30].

A total of seven completed clinical studies that met the inclusion criteria were identified for benralizumab. Castro 2014, Nowak 2015 and Park 2016 were excluded because they were Phase 2 studies that evaluated unlicensed dosing regimens of benralizumab. Study NCT01947946 was excluded as it was terminated with 13 randomised patients and no results were available.

Table 4 Summary of identified benralizumab clinical trials in patients with severe asthma

Study name	Study phase	Sample size (N)	Interventions	Description
SIROCCO (NCT01928771) [11]	Phase III	1,205	Benralizumab; 30 mg Q4W Benralizumab; 30 mg Q8W Placebo	Efficacy and safety study of benralizumab added to high-dose ICS plus LABA in patients with uncontrolled asthma
CALIMA (NCT01914757) [12]	Phase III	1,306	Benralizumab; 30 mg Q4W Benralizumab; 30 mg Q8W Placebo	Efficacy and safety study of benralizumab added to medium-dose or high-dose ICS plus LABA in patients with uncontrolled asthma
ZONDA (NCT02075255) [13]	Phase III	220	Benralizumab; 30 mg Q4W Benralizumab; 30 mg Q8W Placebo	Reducing OCS use in patients with uncontrolled asthma on high dose ICS plus LABA and chronic OCS therapy
Castro 2014 (NCT01238861) [31]	Phase II	609	Benralizumab; 2 mg Benralizumab; 20 mg Benralizumab; 100 mg Placebo	Efficacy study of multiple subcutaneous doses of benralizumab or placebo in adult patients with uncontrolled asthma
Park 2016 (NCT01412736) [32]	Phase II	106	Benralizumab; 2 mg Benralizumab; 20 mg Benralizumab; 100 mg Placebo	Efficacy study of the effect of multiple subcutaneous doses of benralizumab on the annual asthma exacerbation rate in adult patients with uncontrolled, suspected eosinophilic asthma
Nowak 2015 (NCT00768079) [33]	Phase II	110	Benralizumab 0.3 mg/kg Benralizumab 1 mg/kg Placebo	Efficacy study of single intravenous doses of benralizumab in adult patients who required an urgent healthcare visit for treatment of an acute asthma exacerbation
NCT01947946	Phase II	13	Benralizumab; 30 mg Q4W Benralizumab; 30 mg Q8W Placebo	Efficacy and safety study of benralizumab added to medium-dose ICS plus LABA in patients with uncontrolled asthma – this trial was terminated due to sponsor decision

Source: company submission section B.2.1 p. 65

4.1.4.1 Summary description of included studies

The evidence for benralizumab within the CS was based mainly on data from three Phase III randomised controlled trials (RCTs) comparing benralizumab against placebo plus standard of care (SoC) in patients with severe asthma. Two trials (SIROCCO and CALIMA) used a primary endpoint of reduction in exacerbations, while the third trial (ZONDA) enrolled patients receiving oral corticosteroids and used a primary endpoint of reduction in corticosteroids. The inclusion of these three trials appeared to be appropriate since they assessed the licensed dose (30 mg Q8W) and included patients with severe asthma, which

was eosinophilic in nature in some or all patients. The trials also assessed the effect of benralizumab as an add-on treatment, with patients continuing to receive their background asthma controller treatments at a stable dosage during the studies.

ZONDA (SB-240563/046, Nair et al., 200933) was a 26-week OCS sparing trial, that aimed to confirm if benralizumab can reduce OCS dependence (after dose optimisation) in patients who are uncontrolled on high-dose ICS plus LABA, and chronically dependent on OCS.

Two different dosing regimens were evaluated in the above Phase 3 trials. In line with the licensed indication, the focus of the submission was on the licensed dose (Q8W). While full ITT results were presented in the submission, the focus of the submission was on patient subgroup with blood eosinophil count ≥300 cells per µl, and either ≥3 exacerbations needing systemic corticosteroids in the past 12 months, or ≥6 months previous treatment with OCS.

4.1.4.1.1 Design of included RCTs

Summary of methodology of RCTs

The three included benralizumab RCTs are described in Table 5.

1. **SIROCCO**

   SIROCCO (NCT01928771), Bleeker et al., 2016) was a Phase III, double-blind, 48-week, dose-ranging RCT comparing benralizumab (30 mg every 4 weeks (Q4W) or 30 mg every 8 weeks (Q8W); first 3 doses given 4 weeks apart) versus placebo in patients (12 years to 75 years) with severe uncontrolled asthma. The ERG's report focused on data from the Q8W group since this was stated in the CS to be in line with licensed indication. The primary endpoint was clinically significant asthma exacerbations. Patients could enter the trial if they had a diagnosis of asthma (for at least one year) and at least two documented asthma exacerbations while on high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS plus LABA) in the previous year.

2. **CALIMA**

   CALIMA (NCT01914757, Fitzgerald 2016) was a Phase III, double-blind, 56-week RCT comparing benralizumab (30 mg every 4 weeks (Q4W) or 30 mg every 8 weeks (Q8W) versus placebo. Participants (aged 12 years to 75 years) had severe, uncontrolled, eosinophilic asthma, defined as blood eosinophil count ≥300 cells/µL in the 12 months prior to screening or ≥150 cells/µL at screening. The primary endpoint was clinically significant asthma exacerbations. Patients could enter the trial if they had a diagnosis of asthma (for at least one year) and at least two documented

asthma exacerbations while on medium-dosage to high-dosage inhaled corticosteroids plus long-acting β2-agonists (ICS plus LABA) in the previous year.

3. **ZONDA**

ZONDA (NCT02075255, Nair et al., 2017) was a Phase III, double-blind, 28-week RCT comparing benralizumab 30 mg every 4 weeks (Q4W) or 30 mg every 8 weeks (Q8W); (first 3 doses given 4 weeks apart) versus placebo in patients with severe asthma which was likely to be eosinophilic. All participants were also receiving mOCS. There was a run-in phase prior to randomisation to ensure patients were receiving the lowest dose of corticosteroids that would maintain asthma control, and patients were eligible to be randomised if they had achieved a stable dose of OCS at the end of the run-in phase. The primary endpoint was reduction in OCS dose. The ERG note that the study included patients with fewer than 3 exacerbations.

Table 5 Clinical effectiveness evidence

Trial	**SIROCCO (NCT01928771)**	**CALIMA (NCT01914757)**	**ZONDA (NCT02075255)**
Trial design	Randomised, Double-blind, Parallel Group, Placebo controlled	Randomised, Double-blind, Parallel Group, Placebo controlled	Randomised, Double-blind, Parallel Group, Placebo controlled
Key eligibility criteria for participants*	• Aged 12–75 years • Weight at least 40 kg • 2 or more asthma exacerbations in prior year • Uncontrolled asthma receiving high-dose ICS plus LABA with/without additional asthma controller(s)	• Aged 12–75 years • Weight at least 40 kg • 2 or more asthma exacerbations in prior year • Uncontrolled asthma receiving medium to high-dose ICS plus LABA with/without additional asthma controller(s)	• Aged 18-75 years • Receiving high-dose ICS plus LABA and chronic OCS with or without additional asthma controller(s) • Blood eosinophils ≥150 cells/μL • 1 or more asthma exacerbations in prior year
Settings and locations where the data were collected	374 centres in 17 countries, including 24 UK centres	303 centres in 11 countries	89 centres in 12 countries
Trial drugs	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo^	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo^	Benralizumab 30 mg/mL SC, every 4 weeks, or every 4 weeks for the first three doses and every 8 weeks thereafter (with matching placebo at the 4 week interim to maintain blinding), or matching placebo
Permitted and disallowed concomitant medication	Patients continued to receive any other asthma-controller medications	Patients continued to receive any other asthma-controller medications	Patients continued to receive any other asthma-controller medications

Primary outcomes	Annual asthma exacerbation rate ratio versus placebo	Annual asthma exacerbation rate ratio versus placebo	Percentage reduction in oral glucocorticoid dose from baseline to week 28
Other outcomes used in the economic model/specified in the scope	Prebronchodilator FEV_1, total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48, time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events	Prebronchodilator FEV_1, total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 56, time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events	% of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase, and the % of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained. Annual asthma exacerbation rate, time to the first asthma exacerbation, percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalisation), FEV_1 before bronchodilation, total asthma symptom score, ACQ-6 score, AQLQ(S)+12 score, EQ-5D, WPAI, healthcare resource utilisation, adverse events
Pre-planned subgroups	• Baseline OCS use • Sex • Age • Geographic region • Body mass index • Number of exacerbations in the previous year • Race • Nasal polyps at baseline • Immunoglobulin E at baseline • Atopic asthma at baseline • Prior treatment with omalizumab • Blood eosinophil levels	• Baseline OCS use • Sex • Age • Geographic region • Body mass index • Number of exacerbations in the previous year • Race • Nasal polyps at baseline • Immunoglobulin E at baseline • Atopic asthma at baseline • Prior treatment with omalizumab • Blood eosinophil levels	• Age • Gender • Body mass index • Number of exacerbations in the previous year • Geographical region • OCS dose at baseline • Blood eosinophil levels

Source: company submission Section B.2.2 table 11, p.67

4.1.5 Quality assessment

Table 6 Full quality assessment for clinical trials considered for inclusion

Study name	Jadad score	Allocation concealment grade	Randomisation and Allocation concealment	Baseline characteristics	Blinding	Withdrawal	Outcome selection and reporting	Statistical analysis
SIROCCO study (Bleecker 2016)	5	A	Low risk; Randomisation and allocation concealment was carried out by IVRS method.	Low risk; Baseline characteristics were comparable between the treatment groups.	Low risk; This was a double-blind study. Blinding was achieved by matching placebo.	Low risk; The withdrawals, completers, and the specific reasons for withdrawals were reported.	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry NCT01928771.	Low risk; ITT population was used for efficacy and mITT for safety outcomes.
CALIMA study (Fitzgerald 2016)	5	A	Low risk; The randomisation and allocation concealment was carried out using interactive web-based voice response system	Low risk; Baseline characteristics were comparable between the treatment groups.	Low risk; This was a double-blind study. Blinding was achieved by matching placebo.	Low risk; The withdrawals, completers, and the specific reasons for withdrawals were reported.	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry NCT01914757	Low risk; ITT population was used for both primary efficacy and safety analysis.
ZONDA study (Nair 2017)	5	A	Low risk; The randomisation and allocation concealment was carried out using interactive web-based voice response system	Low risk; Baseline characteristics were comparable between the treatment groups.	Low risk; This is a double-blind study.	Low risk; The withdrawals, completers, and the specific reasons for withdrawals were reported.	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry NCT02075255	Low risk; ITT population was used for both primary efficacy and safety analysis.

Source: Adapted from company submission Appendix D1.3 p. 432

The ERG noted that Jadad scores are not considered reliable measures of quality and so the ERG based their critique of the company's quality assessment on the CRD criteria only. The ERG agreed that the CRD criteria provide a reliable checklist for quality assessment. The ERG agreed with the company judgements for all but one of the criteria assessed. The ERG agreed that all three key studies in the CS (SIROCCO, CALIMA and ZONDA) were appropriately randomised and treatment allocation concealed. Blinding of care providers, participants and outcome assessors to treatment allocation was undertaken in all studies. There were no unexpected imbalances in dropouts between groups in the ITT population. All studies included an analysis described in the CS as "ITT" but which the ERG would define as a well-recognised form of modified ITT (included all patients who were randomised and received at least one dose of study medication). However, the CS mainly focussed on the sub-populations rather than the ITT population. The ERG disagreed with the company in the assessment of the criteria "outcome selection and reporting" for all three trials.

SIROCCO

Table 7 Risk of bias for SIROCCO trial

Item	Company's judgement	ERG's judgement
Was randomisation carried out appropriately?	Yes – each patient assigned unique enrolment number and randomisation code by an interactive web-based voice response system	Yes
Was the concealment of treatment allocation adequate?	Yes – AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation were not aware of the treatment allocation	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – patient demographics and baseline clinical characteristics were balanced across treatment groups and by eosinophil count (at least 300 cells per µl versus less than 300 cells per µl)	Yes

Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation were not aware of the treatment allocation	Yes - Study used "double-blind, double-dummy design." Placebo was visually matched to the Benralizumab solution and participants assigned to the Q8W dosing regimen received placebo doses at intervening visits to maintain blinding of participants and care providers.
Were there any unexpected imbalances in drop-outs between groups?	No – the proportions of patients who discontinued treatment were similar across groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all key pre-specified endpoints were reported in the clinical study reports and/or publications	Yes
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 – all analyses conducted on the ITT population. Sensitivity analyses were conducted to assess the impact of missing data Three multiple imputation methods (MAR, partial-DRMI, and DRMI) were used to assess robustness to missing data	Yes - For all key outcomes mITT population used for analyses (all participants who received at least one dose of assigned study drug included in analyses)

For SIROCCO, the ERG had concerns regarding selective reporting of outcomes resulting in reporting bias. The SIROCCO clinical trial protocol listed 23 endpoints to be investigated, however data for many of these outcomes were not reported in the referenced paper or online appendices, although they are reported in the clinical study report. Because the clinical study report is not published in the public domain and is only available by request to the company, the ERG considered that this restriction constitutes reporting bias. The key efficacy outcome of interest for this trial was annual asthma exacerbation rate. The missing outcomes of change in asthma rescue medication, PEF assessment and night awakening due to asthma were considered by the ERG to be relevant to the primary outcome. Data from the SIROCCO CSR

[redacted]. Data from the CSR also

[redacted]

Data reported in the CSR

Therefore these data from the SIROCCO trial suggested

The ERG's clinical expert, David Halpin, advised that most clinicians would not consider

113

113.

These data from the SIROCCO trial suggested

CALIMA

Table 8 Risk of bias assessment for CALIMA trial

Item	Company's judgement	ERG's judgement
Was randomisation carried out appropriately?	Yes – each patient assigned unique enrolment number and randomisation code by an interactive web-based voice response system	Yes
Was the concealment of treatment allocation adequate?	Yes – AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation were not aware of the treatment allocation	Yes
Were the groups similar at the outset of the study	Yes – patient demographics and baseline clinical characteristics were balanced across treatment groups and	Yes

in terms of prognostic factors?	by eosinophil count (at least 300 cells per µl versus less than 300 cells per µl)	
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – placebo solution was visually matched with benralizumab solution. Both benralizumab and placebo were provided in an accessorised pre-filled syringe	Yes - Study used "double-blind, double-dummy design." Placebo was visually matched to the benralizumab solution and participants assigned to the Q8W dosing regimen received placebo doses at intervening visits to maintain blinding of participants and care providers.
Were there any unexpected imbalances in drop-outs between groups?	No – the proportions of patients who discontinued treatment were similar across groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all key pre-specified endpoints were reported in the clinical study reports and/or publications	Yes
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 – all analyses conducted on the ITT population. Sensitivity analyses were conducted to assess the impact of missing data Three multiple imputation methods (MAR, partial-DRMI, and DRMI) were used to assess robustness to missing data	Yes - Primary endpoint analysis used intention-to-treat analysis.

Incomplete data reporting was also a concern in the CALIMA trial. Endpoints outlined in the protocol that are not reported in either trial publication or appendices included change in asthma rescue medication use, PEF assessment of lung function, night awakening due to asthma, pharmacokinetics, extent of exposure, EQ-5D-5L VAS scores, work productivity loss, productivity loss in the classroom, utilization of healthcare resources, and patient and clinician assessment of response to treatment.

[redacted]

[redacted]

ZONDA

Table 9 Risk of bias for ZONDA trial

Item	Company's judgement	ERG's judgement
Was randomisation carried out appropriately?	Yes – each patient assigned unique enrolment number and randomisation code by an interactive web-based voice response system	Yes
Was the concealment of treatment allocation adequate?	Yes – AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation were not aware of the treatment allocation	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline characteristics were balanced between arms, with the exception of median baseline blood eosinophil count, which was lower in the benralizumab 30 mg Q4W and Q8W groups compared with the placebo group	The distribution of patients according to the clinically important eosinophil groups (≥150 to <300 cells/mm^3 and ≥300 cells/mm^3) were similar between benralizumab Q8W and placebo groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – placebo solution was visually matched with benralizumab solution. Both benralizumab and placebo were provided in an accessorised pre-filled syringe.	Yes- "Investigators and patients were unaware of the trial-group assignments." No reference to visually matching placebo and benralizumab identified. Participants assigned to the 8week dosing regimen received placebo doses at intervening visits to maintain blinding of participants and care providers.
Were there any unexpected imbalances in drop-outs between groups?	No – the proportions of patients who discontinued treatment were similar across groups	No
Is there any evidence to suggest that the authors	No – all key pre-specified endpoints were reported in the clinical study	Yes

measured more outcomes than they reported?	reports and/or publications	
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 – all analyses conducted on the ITT population. Sensitivity analyses to account for missing data were not conducted due to the low proportion of missing data	Yes - all analyses conducted on the ITT population.

The ERG disagreed with AstraZeneca's assessment of risk of bias in the ZONDA trial with regard to one item. The ERG had concerns about selective outcome reporting in the ZONDA trial. The clinical trial protocol listed one primary outcome and 33 secondary outcomes, many of which were not reported in the CS and its appendices. Asthma rescue medication use and nocturnal awakening were, again, among the missing endpoints.

[redacted]

Generalisability of SIROCCO, CALIMA, ZONDA to UK clinical practice

The ERG considered the standard care in all three trials consistent with current UK guidelines/clinical practice.

4.1.5.1 Statistical analysis in included studies

Table 10 Summary of statistical analysis

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SIROCCO	Assess differences in exacerbation rates between benralizumab and placebo	ITT analysis using a negative binomial model for the primary endpoint, with adjustment for treatment, region, exacerbations in the previous year (two, three, or four or more), and OCS use	252 patients with blood eosinophil counts ≥300 cells per µl per treatment group (756 total) were needed for 90% power to detect a 40% reduction in annual exacerbation rate in both benralizumab dosage regimens compared with placebo	Patients who discontinued the study were followed up for subsequent visits. Sensitivity analyses were conducted to assess the impact of missing data on the primary and key secondary endpoints
CALIMA			228 patients with blood eosinophil counts ≥300 cells per µl per treatment group (684 total) were needed to achieve 90% power to detect a 40% reduction in the annual asthma exacerbation rate for both benralizumab dosage regimens versus placebo	
ZONDA	Assess differences in OCS dose reduction between benralizumab and placebo	ITT analysis using a Wilcoxon rank-sum test for the primary endpoint	70 patients per group was needed to achieve 86% power to detect a difference in the primary endpoint between each benralizumab group and placebo	The proportion of patients with missing data was low and similar across treatment groups; sensitivity analysis to assess the impact of missing data was not conducted

Source: company submission Table 16 Section B.2.4 p. 83

For SIROCCO and CALIMA, the primary efficacy endpoint - the annual asthma exacerbation rate ratio versus placebo - was analysed using a negative binomial model, with adjustment for treatment, region, exacerbations in the previous year (two, three, or four or more), and oral corticosteroid use at time of randomisation. This is an accepted approach for the analysis of exacerbation rates in severe asthma according to previous research. A post-hoc analysis was conducted to assess the treatment effect of a history of at least three exacerbations experienced by patients in the previous year using a separate negative binomial model with adjustment for treatment, region, oral corticosteroid use, and number of previous exacerbations.

Analysis of FEV_1, ACQ scores and AQLQ scores were performed using a mixed-effects model for repeated measures analysis, with adjustment for treatment, region, baseline value, oral corticosteroid use at time of randomisation, visit, and visit x treatment.

All efficacy analyses were conducted on the intention-to-treat (ITT) population.

In SIROCCO and CALIMA, for the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. Sensitivity analysis were conducted to assess the impact of missing data on the primary and key secondary endpoints. Three multiple imputation methods (missing at random (MAR), partial-dropout reason-based multiple imputation [partial-DRMI], and DRMI) were used to assess robustness to missing data for these endpoints. MAR assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment. The results of all three methods were consistent with the results of the primary efficacy analysis, indicating that the results of the studies were robust to missing data. The ERG was satisfied that the potential impact of missing data following withdrawal on the results of the analyses has been considered appropriately.

In ZONDA, the primary efficacy endpoint was the percentage reduction in OCS dose at week 28 compared to the baseline dose, whilst maintaining asthma control. Benralizumab was compared to placebo using a Wilcoxon rank-sum test. A sensitivity analysis for the assessment of the primary endpoint was conducted with a proportional-odds model, with controls for trial group, geographic region and baseline oral glucocorticoid dose. Missing data were assumed to be missing at random.

A Cochran-Mantel-Haenszel test, with adjustment for geographic region, was used to analyse secondary endpoints regarding reductions in the oral glucocorticoid dose categorised as follows:

10% or more reduction, 25% or more reduction, 50% or more reduction, or 100% reduction (discontinuation of OCS therapy). This was analysed using a negative binomial model, with adjustment for trial group, geographic region, and number of exacerbations in the previous year, and an offset term of the logarithm of the follow-up time was used to calculate annual exacerbation rates in the trial groups.

All participants in the ITT population were included in the ITT analysis. In ZONDA, the proportion of patients with missing data was low and similar across treatment groups, and the optional sensitivity analysis to assess the impact of missing data was not conducted.

The CS provided details of sensitivity analysis to assess the impact of missing data on primary and key secondary end points in SIROCCO and CALIMA using three multiple imputation methods (MAR, partial-DRMI and DRMI), presumably for the ITT analyses (CS, p.90). The CS states that the proportion of patients with missing data was low and similar

across treatment groups in ZONDA, and the optional sensitivity analysis to assess the impact of missing data was not conducted in ZONDA (CS p.90).

4.1.5.2 Statistical methods for subgroup analyses

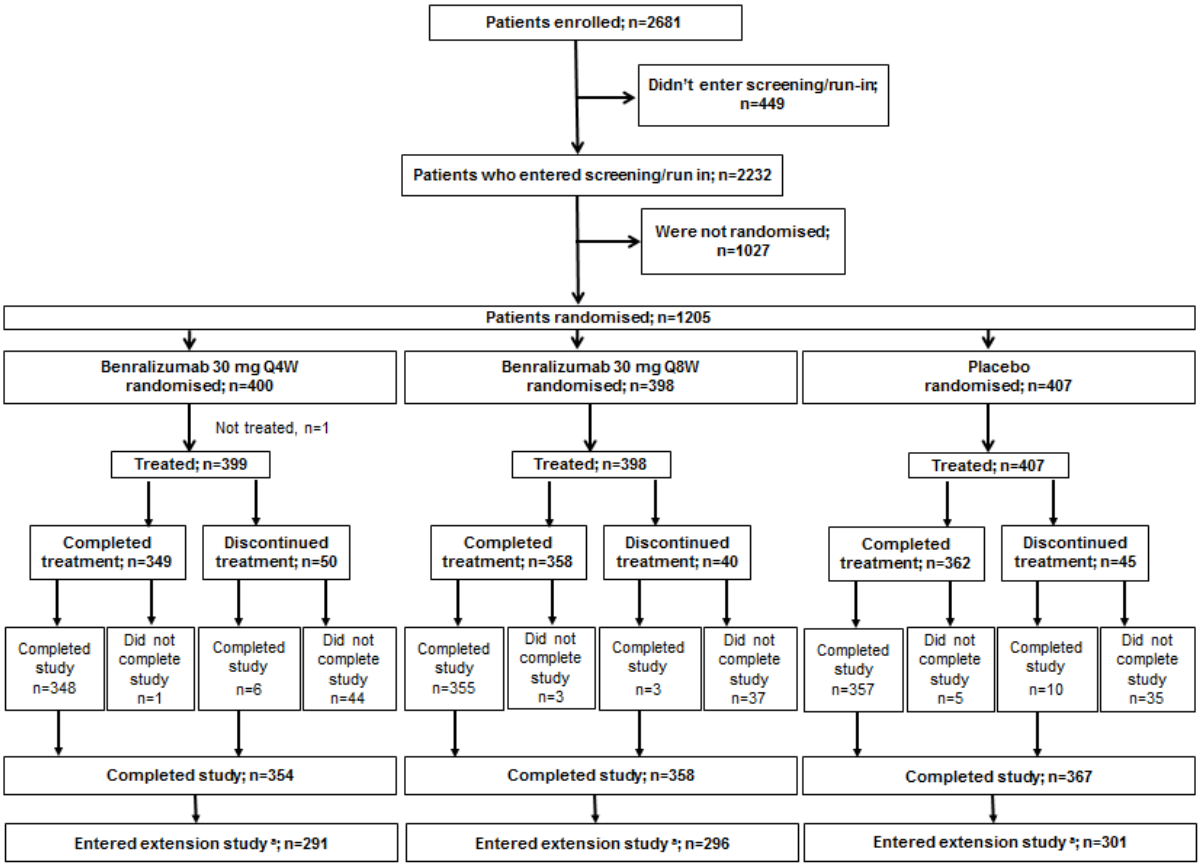
In SIROCCO and CALIMA, pre-specified subgroup analyses assessed the exacerbation rate in subgroups of clinical relevance. A post-hoc analysis was also conducted in the primary analysis population for the purposes of the CS, to assess the treatment effect of a history of at least three exacerbations experienced by patients in the previous year using a separate negative binomial model with adjustment for treatment, region, oral corticosteroid use, and number of previous exacerbations.

In ZONDA, an exploratory subgroup analysis of patients with blood eosinophils ≥300 cells per µl was conducted. Results for exploratory variables were analysed with the use of descriptive statistics according to trial group.

4.1.5.3 Participant flow in included studies (ITT populations)

The numbers of patients screened and randomised in the ITT populations of the three benralizumab RCTs are shown in Figure 3, Figure 4, and Figure 5

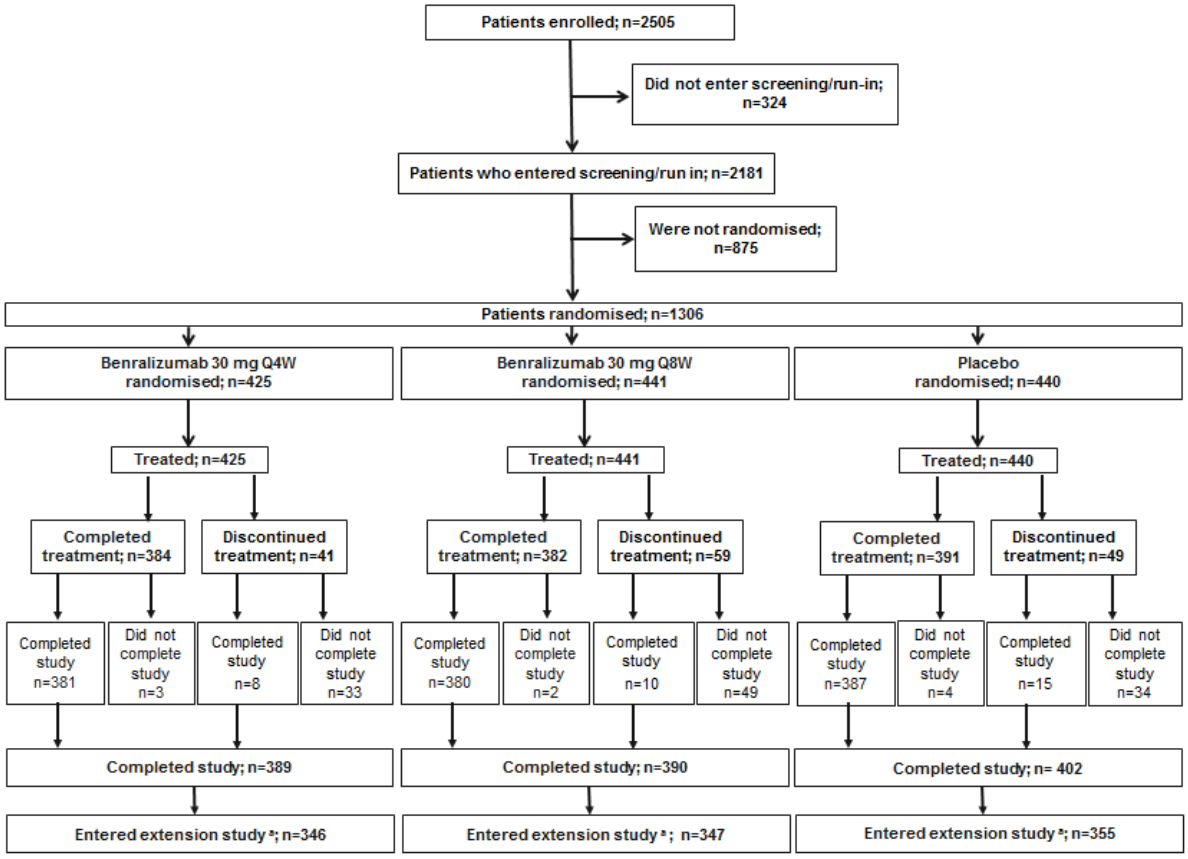
Figure 3 Participant flow in the SIROCCO trial



Source: company submission section B.2.4 Figure 13 p. 91

In SIROCCO, 2232 patients were screened, 1205 (54%) were randomised and 1204 formed the ITT population (randomised and received study medications; this is actually a form of modified ITT [mITT] but this population is referred to in the ERG's report as the ITT population for consistency with the CS). Of these, 1069 (88.7%) completed the study, 135 (11.2%) discontinued treatment and 22 (1.8%) withdrew due to adverse events (AEs). In addition, patients were eligible to continue treatment in an open-label BORA safety extension study.

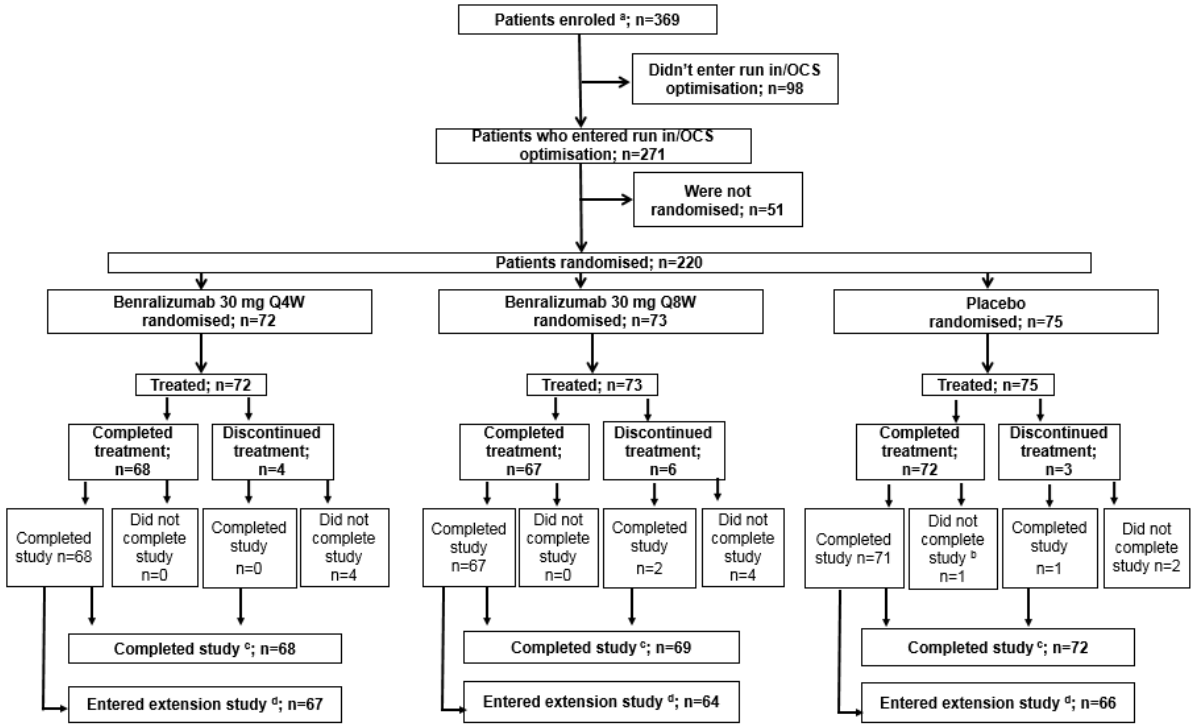
Figure 4 Participant flow in the CALIMA trial



Source: company submission section B.2.4 Figure 14 p. 92

In CALIMA, 2181 patients were screened, 1306 (59.9%) were randomised and all 1306 formed the ITT population. Of these, 1157 (88.6%) completed treatment with study drug. 149 (11.4%) patients discontinued treatment and 22 (1.7%) withdrew due to AEs. In addition, patients were eligible to continue treatment in an open-label BORA safety extension study.

Figure 5 Participant flow in the ZONDA trial



Source: company submission section B.2.4 Figure 15 p. 93

In ZONDA, 271 patients were screened, 220 (81.2%) were randomised and all 220 formed the ITT population. Of these, 207 (94.1%) patients completed treatment with study drug. 13 (5.9%) patients discontinued treatment and 5 (2.3%) withdrew due to AEs .

The ERG note that while the rate of participant withdrawal was consistent across the three arms in all three studies, participant withdrawal was high in SIROCCO and CALIMA, 136 (11%) and 149 (11%) participants lost respectively, compared to 11 (5%) participants lost in ZONDA.

4.1.5.4 Baseline characteristics of patients in included RCTs

The ERG considered patients in all three RCTs to be representative of UK clinical practice. For the SIROCCO (Table 11) and CALIMA (Table 12) trials, patient demographics and baseline clinical characteristics were balanced across treatment groups and by eosinophil count (at least 300 cells per µl versus less than 300 cells per µl). Baseline characteristics were balanced for patients on high-dose ICS plus LABA with baseline blood eosinophils ≥300 cells per µl, which is the subgroup informing the economic model

Table 11 Baseline patient characteristics in the SIROCCO trial

	All patients (n=1204)			**High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µl (n=809)**		
	Placebo (n=407)	**Benralizumab 30mg Q4W** (n=399)	**Benralizumab 30mg Q8W** (n=398)	**Placebo** (n=267)	**Benralizumab 30mg Q4W** (n=275)	**Benralizumab 30 mg Q8W** (n=267)
Age (years)	48.7 (14.9)	50.1 (13.4)	47.6 (14.5)	48.6 (14.7)	49.2 (13.1)	47.6 (14.6)
Sex						
Male	138 (34%)	124 (31%)	146 (37%)	87(33%)	102 (37%)	93 (35%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)
Race						
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)
Other	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)
Hispanic or Latino ethnicity	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)
BMI (kg/m^2)	28.9 (7.1)	29.2 (7.1)	28.2 (6.2)	28.7 (7.0)	28.9 (6.9)	27.7 (6.1)
Eosinophil count (cells per µl)	370 (0-2690)	390 (0-3440)	360 (0-3100)	500 (300-2690)	500 (300-3440)	500 (300-3100)

Central eosinophil count (cells per µL)	350 (0-3580)	360 (0-3170)	325 (0-3110)	480 (70-2220)	470 (40-3170)	460 (10-3110)
Prebronchodilator FEV1 (L)	1.660 (0.584)	1.655 (0.553)	1.680 (0.582)	1.654 (0.580)	1.673 (0.577)	1.660 (0.574)
Predicted normal	56.6% (15.0)	57.4% (14.1)	56.1% (14.6)	56.4% (14.6)	56.5% (14.4)	55.5% (14.6)
Prebronchodilator FEV1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)
Reversibility	20% (−26 to 154)	18% (−7 to 136)	22% (−12 to 157)	20% (−26 to 154)	18% (−7 to 136)	21% (−10 to 157)
ACQ-6 score†	2.87 (0.94)	2.77 (0.96)	2.80 (0.88)	2.90 (0.95)	2.77 (0.95)	2.81 (0.89)
Time since asthma diagnosis (years)	14.2 (1.1–72.4)	15.3 (1.1–70.4)	14.4 (1.1–66.9)	13.4 (1.1–65.2)	14.9 (1.1–62.6)	14.6 (1.1–66.9)
Number exacerbations in past 12 months	3.0 (1.8)	2.9 (1.8)	2.8 (1.5)	3.1 (2.0)	3.0 (2.0)	2.8 (1.5)
2%	244 (60.0)	253 (63.4)	252 (63.3)	149 (55.8)	173 (62.9)	164 (61.4)
3%	76 (18.7)	64 (16.0)	79 (19.8)	53 (19.9)	44 (16.0)	53 (19.9)
≥4 (%)	87 (21.4)	82 (20.6)	67 (16.8)	65 (24.3)	58 (21.1)	50 (18.7)
Number resulting in ED visit	0.3 (0.8)	0.3 (1.0)	0.2 (0.8)	0.3 (0.8)	0.4 (1.0)	0.3 (0.9)
Patients with ≥1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)

Number resulting in hospital admission	0.4 (0.8)	0.4 (0.7)	0.4 (0.8)	0.4 (0.8)	0.3 (0.7)	0.4 (0.9)
Patients with ≥1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)
Total asthma symptom score	2.68 (1.07)	2.72 (1.02)	2.70 (1.11)	2.74 (1.08)	2.67 (1.01)	2.68 (1.09)
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)
AQLQ(S)+12 score‡	3.90 (1.02)	3.93 (0.98)	3.94 (1.00)	3.87 (0.99)	3.93 (1.00)	3.93 (0.97)
Current smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Nicotine pack-years	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	6.0 (0–9)	5.0 (0–9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. Missing data are not accounted for in this table. ICS=inhaled corticosteroids. LABA=long-acting β2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity.
§ Current smoker or former smoker with a smoking history of ≥10 packs per year.
* Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other.
† Low numbers represent better symptom control.
‡ High numbers suggest better quality of life.
Source: company submission Section B.2.3 table 13, p. 78

Table 12 Baseline patient characteristics in the CALIMA trial

	All patients (n=1306)			**High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µl (n=728)**		
	Placebo (n=440)	**Benralizumab 30mg Q4W** (n=425)	**Benralizumab 30mg Q8W** (n=441)	**Placebo (n=248)**	**Benralizumab 30mg Q4W** (n=241)	**Benralizumab 30 mg Q8W** (n=239)
Age (years)	48.8 (15.1)	50.0 (13.6)	49.0 (14.3)	48.5 (14.1)	50.1 (13.1)	49.6 (13.0)
Sex						
Male	176 (40%)	155 (36%)	168 (38%)	103 (42%)	82 (34%)	101 (42%)
Female	264 (60%)	270 (64%)	273 (62%)	145 (58%)	159 (66%)	138 (58%)
White	372 (85%)	360 (85%)	369 (84%)	213 (86%)	209 (87%)	203 (85%)
Black or African American	14 (3%)	10 (2%)	15 (3%)	8 (3%)	5 (2%)	8 (3%)
Asian	53 (12%)	55 (13%)	55 (12%)	27 (11%)	27 (11%)	28 (12%)
Other	1 (<1%)	0	2 (<1%)	0	0	0
Hispanic or Latino ethnicity	92 (21%)	104 (24%)	104 (24%)	52 (21%)	56 (23%)	52 (22%)
BMI (kg/m^2)	28.9 (6.5)	28.7 (6.8)	28.8 (6.5)	29.0 (6.1)	29.1 (7.3)	28.6 (6.1)
Eosinophil count (cells per µl)	371 (0–4494)	370 (20–2420)	400 (0–2600)	510 (300–4494)	500 (300–2420)	500 (300–2600)
Central eosinophil count (cells per µL)	370 (0–4150)	350 (0–2800)	350 (0–2260)	490 (30–4150)	470 (0–2800)	475 (10–2260)
Prebronchodilator FEV1 (L)	1.771 (0.645)	1.757 (0.602)	1.759 (0.641)	1.815 0.648)	1.75 (0.570)	1.758 (0.622)

Predicted normal	58.0% (14.9)	58.9% (14.8)	57.9% (14.9)	58.2% (13.9)	59.1% (13.7)	57.0% (14.2)
Prebronchodilator FEV1/FVC	61 (13)	61 (12)	60 (13)	60 (12)	61 (12)	60 (13)
Reversibility	20% (−18 to 814)	20% (−24 to 809)	20% (−13 to 171)	20% (−9 to 133)	20% (−24 to 124)	20% (−13 to 171)
ACQ-6 score†	2.69 (0.92)	2.69 (0.91)	2.75 (0.93)	2.75 (0.94)	2.70 (0.91)	2.80 (0.95)
Time since asthma diagnosis (years)	16.2 (1.2–69.9)	15.8 (1.2–69.2)	16.8 (1.1–64.6)	17.0 (1.3–69.9)	15.6 (1.3–66.2)	16.1 (1.2–58.2)
Number exacerbations in past 12 months	2.7 (1.6)	2.7 (1.9)	2.7 (1.4)	2.8 (1.7)	2.8 (1.7)	2.7 (1.3)
2%	288 (65.5)	280 (65.9)	287 (65.1)	151 (60.9)	148 (61.4)	144 (60.3)
3%	93 (21.1)	89 (20.9)	93 (21.1)	56 (22.6)	54 (22.4)	59 (24.7)
≥4 (%)	59 (13.4)	55 (12.9)	60 (13.6)	41 (16.5)	38 (15.8)	36 (15.1)
Number resulting in ED visit	0.3 (1.2)	0.3 (0.8)	0.2 (0.7)	0.4 (1.4)	0.3 (0.9)	0.2 (0.6)
Patients with ≥1 exacerbations resulting in ED visit	62 (14%)	60 (14%)	56 (13%)	36 (15%)	35 (15%)	31 (13%)
Number resulting in hospital admission	0.3 (0.8)	0.2 (0.5)	0.3 (0.7)	0.3 (0.7)	0.2 (0.5)	0.3 (0.6)

Patients with ≥1 exacerbations resulting in hospital admission	72 (16%)	65 (15%)	78 (18%)	44 (18%)	42 (17%)	43 (18%)
Total asthma symptom score	2.71 (1.04)	2.73 (1.02)	2.79 (1.06)	2.71 (1.06)	2.69 (0.98)	2.76 (1.06)
Diagnosis of allergic rhinitis	248 (56%)	242 (57%)	227 (51%)	147 (59%)	136 (56%)	125 (52%)
Nasal polyps	73 (17%)	59 (14%)	65 (15%)	55 (22%)	40 (17%)	53 (22%)
Atopic (based on Phadiatop test)	286 (65%)	264 (62%)	278 (63%)	164 (66%)	151 (63%)	149 (62%)
History of omalizumab treatment	14 (3%)	12 (3%)	12 (3%)	9 (4%)	7 (3%)	7 (3%)
AQLQ(S)+12 score‡	3.96 (1.03)	3.98 (0.96)	3.85 (1.02)	3.93 (1.04)	3.99 (0.98)	3.87 (1.05)
Smoking history						
Never	349 (79%)	325 (76%)	348 (79%)	203 (82%)	175 (73%)	185 (77%)
Current	2 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)
Former	89 (20%)	100 (24%)	90 (20%)	44 (18%)	66 (27%)	53 (22%)
Smoking pack year (years)	5 (0–9)	5 (0–9)	5 (0–45)	4 (0–9)	5 (0–9)	4.5 (0–45)

Data are mean (SD), median (range), or n (%). ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroids. LABA=long-acting β2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).
*Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other.
†Data not available for all randomised patients.
‡The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β2-agonist use on a 0–6 scale (low numbers represent better control).
§The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale (greater numbers indicate better quality of life).
¶For current and former smokers. Missing data are not presented.

Source: company submission Section B.2.3 table 14, p. 81

In the SIROCCO trial, use of maintenance asthma treatment was similar across groups, with a mean fluticasone propionate or equivalent total daily dosage of 899 µg (range 125-3000). Overall, 196 (16%) patients were receiving oral corticosteroids, with similar dosing between cohorts.

In the ZONDA trial, baseline characteristics of the intention to treat population were balanced between arms, with the exception of the median baseline blood eosinophil count, which was lower in the benralizumab 30 mg Q4W and Q8W groups compared with the placebo group (Table 13)

Table 13 Baseline patient characteristics in the ZONDA trial

Characteristic	Placebo (N=75)	Benralizumab Q4W (N=72)	Benralizumab Q8W (N=73)
Age (years)	49.9±11.7	50.2±12.0	52.9±10.1
Female sex, n (%)	48 (64)	40 (56)	47 (64)
White race, n (%)	70 (93.3)	69 (95.8)	66 (90.4)
BMI (kg/m^2)†	28.7±5.2	29.8±6.8	30.2±6.5
Blood eosinophil count			
Median count (range), cells/mm^3 ††	535 (160 - 4550)	462 (160 - 1740)	437 (154 - 2140)
Distribution, n (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)
FEV$_1$ before bronchodilation			
Value, litres	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV$_1$:FVC ratio before bronchodilation, %	62±13	59±13	59±12
Median percent reversibility of FEV$_1$ (range)§	16.4 (-5.4 - 93.4)	18.2 (-3.0 - 126.0)	22.6 (-3.4 - 88.0)
ACQ-6 score ‖	2.7±1.0	2.6±1.1	2.4±1.2
Median time since asthma diagnosis (range), yr	10.5 (1.1 - 54.5)	13.3 (1.2 - 52.3)	16.3 (1.3 - 53.0)
Number of exacerbations in previous 12 months	2.5±1.8	2.8±2.0	3.1±2.8
1	24 (32.0)	24 (33.3)	21 (28.8)
2	22 (29.3)	19 (26.4)	23 (31.5)
3	18 (24.0)	9 (12.5)	9 (12.3)
≥4	11 (14.7)	20 (27.8)	20 (27.4)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Median smoking history (range), pack-yr	6.0 (1 - 9)	5.5 (2 - 9)	5.0 (1 - 8)
Median oral glucocorticoid dose (range), mg/day			

At trial entry‡	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)
At end of run-in phase	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)	10.0 (7.5 - 40.0)
Mean inhaled glucocorticoid dose (range), µg/day	1232 (250 - 5000)	1033 (250 - 3750)	1192 (100 - 3250)
Leukotriene-receptor antagonist, n (%)	25 (33)	28 (39)	29 (40)

* Plus–minus values are means ±SD.
FEV1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.
§ The percentage reversibility of the FEV1 was calculated with the use of FEV1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV1 −prebronchodilation FEV1]÷prebronchodilation FEV1)×100.
¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.
‖ The Asthma Control Questionnaire 6 (ACQ-6)17 is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.
** The Asthma Quality of Life Questionnaire (standardised) for persons 12 years of age or older (AQLQ[S]+12)18 is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.
†† Patients were stratified at randomisation according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.
Source: company submission Section B.2.3 table 15, p. 83

Baseline characteristics in subgroup analysis

A pooled SIROCCO and CALIMA subgroup analysis was performed for adult patients with blood eosinophil level ≥300 cells/µl and ≥3 severe exacerbation, who have failed on high-dose ICS plus LABA therapy. Overall, 24% of patients were on concomitant OCS and 88% on ICS/LABA, and the median time since asthma diagnosis was 16 years (Table 14).

Table 14 Baseline characteristics in the subgroup analysis (pooled SIROCCO and CALIMA)

	Benralizumab 30mg Q8W (N=123)	**Placebo (N=136)**
Age, mean (SD)	50.8 (11.5)	49.6 (12.7)
Female sex, n (%)	74 (60.2)	93 (68.4)
Race, n (%)		
White	91 (74.0)	106 (77.9)
Black or African American	4 (3.3)	2 (1.5)
Asian	25 (20.3)	21 (15.4)
Other	3 (2.4)	7 (5.1)
Years since asthma diagnosis, median (range)	18.4 (1.3, 66.9)	14.3 (1.2, 69.9)
Pre-bronchodilator FEV_1 (L), mean (SD)	1.60 (0.596)	1.67 (0.632)
Local baseline eosinophil count, mean (SD)	718 (475)	676 (450)
N. exacerbations in past 12 months, mean (SD)	4.0 (1.72)	4.4 (2.32)
N. exacerbations leading to hospitalisation or ER treatment in past 12 months, mean (SD)	0.9 (1.69)	0.9 (1.55)
Patients with ≥1 exacerbations resulting in hospitalisation in past 12 months, n (%)	30 (24.4)	33 (24.3)

Diagnosis of allergic rhinitis, n (%)	77 (62.6)	82 (60.3)
Nasal polyps, n (%)	42 (34.1)	43 (31.6)
History of omalizumab treatment, n (%)	13 (10.6)	16 (11.8)
PRO measures		
Total asthma symptom score	2.84 (1.10)	2.82 (1.01)
ACQ-6 score, mean (SD)	2.87 (0.95)	2.90 (0.92)
AQLQ overall, mean (SD)	3.69 (0.99)	3.87 (0.96)
EQ-5D-5L utility score*	0.73 (0.216)	0.75 (0.181)
Maintenance asthma medication use at baseline		
ICS use, n (%)	123 (100.0)	136 (100.0)
Mean ICS total daily dose (µg)(a)	1236.428	1165.788
LABA use, n (%)	122 (99.2)	136 (100.0)
ICS/LABA use, n (%)	110 (89.4)	117 (86.0)
OCS use, n (%)	29 (23.6)	32 (23.5)
Mean OCS total daily dose (mg)(b)	13.845	12.984
LAMA use, n (%)	20 (16.3)	19 (14.0)
LTRA use, n (%)	62 (50.4)	62 (45.6)
Xanthine derivatives use, n (%)	33 (26.8)	27 (19.9)
Other asthma medications use, n (%)	3 (2.4)	1 (0.7)

(a) ICS doses were converted to their Fluticasone Propionate equivalent for this summary.

(b) OCS doses were converted to their Prednisolone equivalent for this summary.

*UK tariff was used to estimate score

Source: company submission section B.2.7 table 22, p. 107

Subgroup analysis was conducted for the ZONDA trial, for patients with blood eosinophils ≥300 cells/ µl (n=125).

[redacted] ([redacted]15).

[redacted]15 [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Source: company submission section B.2.7 table 24 p.110

4.1.6 Applicability to clinical practice

The ERG agreed with the CS that results from the phase 3 trials included in the CS were broadly applicable to clinical practice in England. Maintenance therapy at baseline in the Phase 3 clinical trials was in-line with recommended UK guidelines, i.e. high-dose ICS plus LABA ± OCS based on BTS/SIGN recommendations, and patients continued to receive their asthma-controller medications concomitantly throughout the trials. Clinical advice received by the ERG supported the view that severe uncontrolled asthma would be treated with high-dose ICS according to UK clinical practice guidelines. The ERG noted, however, that CALIMA also recruited patients treated with medium-dose ICS.

The ERG considered standard of care in all three trials to be consistent with current UK guidelines/clinical practice. SIROCCO and CALIMA reported that patients continued to used their background asthma controller medications at a stable dose throughout the study and short acting β2-agonists were permitted as rescue medication where required. Listed concomitant medications included ICS, LABA, ICS/LABA, OCS, LABA (Long-acting β2-agonists), LAMA (Long-acting muscarinic receptor-antagonists), LTRA (Leukotriene receptor antagonists) and Xanthine derivatives. ZONDA reported that patients continued prescribed high-dose glucocorticoid and LABA therapies, as well as additional asthma-controller medications (including leukotriene modifiers, long-acting muscarinic antagonists, and theophylline) at stable doses throughout the trial. Short acting β2-agonists were permitted as rescue medication.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Clinical effectiveness results for benralizumab

AstraZeneca provided clinical effectiveness results of relevant trials for the population in line with the licensed indication involving adult patients with baseline blood eosinophil count of ≥ 300 per µL and on high dose ICS/LABA with or without OCS. AstraZeneca also indicated the patient subgroup for which a NICE recommendation is sought; patients with blood eosinophil count ≥ 300 per µL and either 1) ≥ 3 exacerbations needing systemic corticosteroids in the past 12 months, or 2) ≥ 6 months previous treatment with OCS.

Model assumptions in the economic model were based on patients' age, patients' weight, proportion of female patients, proportion of patients on maintenance OCS (mOCS) at baseline, asthma-related mortality, exacerbation rates, asthma-related hospitalisation rates, EQ-5D and/or AQLQ(S)+12 scores, steroid sparing effect (ZONDA trial), duration of exacerbations, proportion of patients meeting treatment continuation criteria, and proportion of patients who completed the trials.

SIROCCO

At 48 weeks, the annual asthma exacerbation rate (AER) for the benralizumab group was 0.65 (0.53-0.80) compared to placebo 1.33 (1.12-1.58) per year giving a rate ratio of 0.49 (0.37-0.64; $p < 0.0001$). Benralizumab decreased the AER by 51%. About a third of patients (34.8%) who received benralizumab experienced one or more exacerbations compared to half (50.6%) of patients on placebo.

Improved lung function demonstrated by Least Squares (LS) mean difference of 159mls in the pre-bronchodilator FEV_1 was observed in benralizumab compared to placebo (Figure 6) ($p = 0.0006$). Total asthma symptom score was more reduced in benralizumab group (-1.30) compared to placebo (-1.04) (Table 16). However, the difference in total asthma score reduction (-0.25), though statistically significantly, did not reach Minimum Clinically Important Difference (MCID) defined as score changes of 0.5 point or more for ACQ-6 and AQLQ(S)+12 [13].

[redacted]

Table 16 Primary and key secondary endpoint results in the SIROCCO trial

	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; p value)	-	0.49 (0.37–0.64; <0.0001)
Key secondary endpoints (48 weeks)		
Prebronchodilator FEV_1 (L)†		
Number of patients‡	261	264
LS mean change (number of patients§)	0.239 (233)	0.398 (235)
LS mean difference vs. placebo (95% CI; p value)	-	0.159 (0.068 - 0.249; 0.0006)
Total asthma symptom score†¶		
Number of patients analysed‡	267	263
LS mean change (number of patients§)	−1.04 (180)	−1.30 (178)
LS mean difference vs. placebo (95% CI; p value)	-	−0.25 (−0.45 - −0.06; 0.0118)
EQ-5D		
Number of patients analysed^	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference	[redacted]	[redacted]

EQ-5D= EuroQol 5 dimensions; ICS=inhaled corticosteroids. LABA=long-acting β2-agonsists. Q8W=every 8 weeks (first three doses Q4W). FEV_1=forced expiratory volume in 1 s. LS=least squares.

* Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.

† Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.

‡ Patients with a baseline and at least one post-baseline assessment.

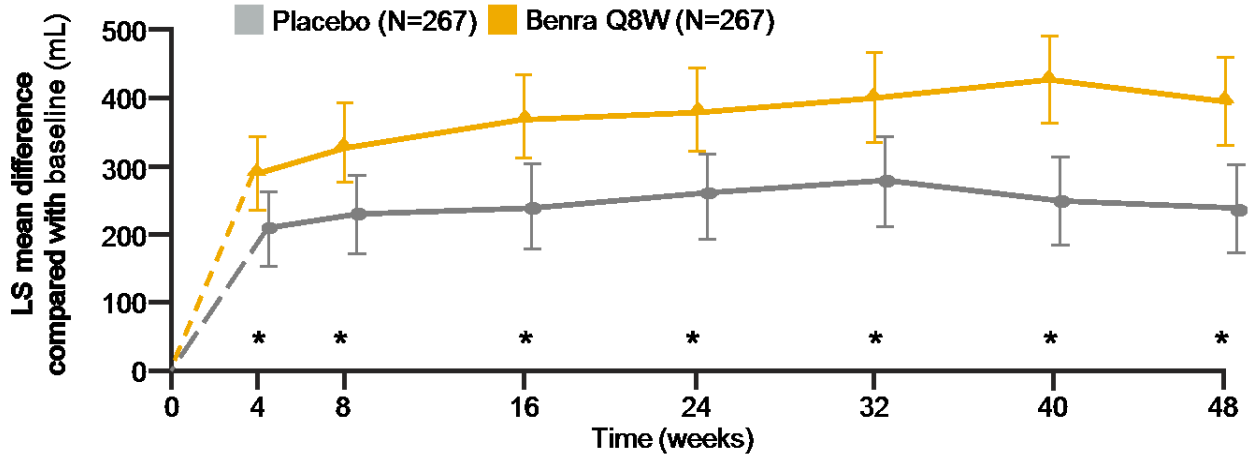
§ Numbers of patients at 48 weeks.

¶ A decrease in score suggests an improvement

^ Excludes adolescents

Source: company submission section B.2.6 table 19, p. 98.

Figure 6 FEV_1 change from baseline through Week 48 in SIROCCO



**P*<0.05 for benra 30 mg Q8 weeks vs. placebo.
Error bars represent 95% confidence intervals. *P* values are from the repeated measures analysis.
Benra=benralizumab; FEV_1=forced expiratory volume in 1 sec; LS=least squares; Q8W=every 8 weeks.
Source: company submission, section B.2.6 figure 16, p. 99

The ERG believe that the analysis of SIROCCO was adequate. Data in this main analysis included also patients with two baseline exacerbations in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations).

CALIMA

At 56 weeks, the AER for benralizumab group was 0.66 (0.54-0.82) compared to placebo was 0.93 (0.77-1.12) per year giving a rate ratio of 0.72 (0.54-0.95; p = 0.0188) (Table 17). Benralizumab decreased the AER by 28%. More than a third (39.7%) of patients who received benralizumab Q8W experienced one or more exacerbations during the study period compared to half (50.8%) of patients who received placebo.

Pre-bronchodilator FEV_1 was improved in benralizumab (LS mean difference versus placebo 116ml; p = 0.0102) (Figure 7). Total asthma symptom score was more reduced for benralizumab (-1.40) than for placebo (-1.16). The difference in total asthma score reduction (-0.23) did not reach MCID.

[redacted]

Table 17 Primary and key secondary endpoint results in the CALIMA trial

	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; p value)	-	0.72 (0.54–0.95; 0.0188)
Key secondary endpoints (48 weeks)		
Prebronchodilator FEV_1 (L)†		
Number of patients‡	244	238
LS mean change (number of patients§)	0.215; 221	0.330; 211
LS mean difference vs. placebo (95% CI; p value)	-	0.116 (0.028–0.204; 0.0102)
Total asthma symptom score†¶		
Number of patients analysed‡	247	237
LS mean change (number of patients§)	−1.16; 187	−1.40; 185
LS mean difference vs. placebo (95% CI; p value)	-	−0.23 (−0.43 to −0.04; 0.0186)
EQ-5D		
Number of patients analysed^	[redacted]	[redacted]
Estimate for groups (95% CI)	[redacted]	[redacted]
Estimate for difference (95% CI; p value)	[redacted]	[redacted]

Data for the primary endpoint are rate estimate (95% CI) or rate ratio (95% CI). Data for the secondary endpoint are mean change from baseline at week 56; n or mean difference (95% CI). EQ-5D= EuroQol 5 dimensions; FEV_1=forced expiratory volume in 1 s. LS=least squares. Q8W=once every 8 weeks (first three doses Q4W).

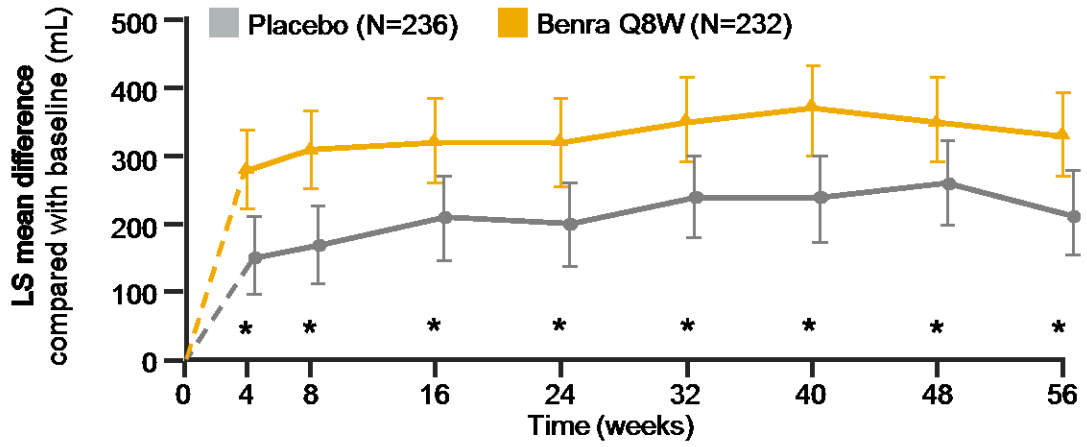
* Estimates calculated using a negative binomial model with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.

† Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.

‡ Key secondary endpoint; composite of daytime and night-time symptoms scored 0–6 overall (a decrease in score indicates improvement).

§ Numbers after semicolon are patients at 56 weeks
^ Excludes adolescents
Source: company submission, section B.2.6 table 20, pp. 99-100

Figure 7 FEV_1 change from baseline through Week 56 in CALIMA



*P<0.05 for Benra 30 mg Q8W.
Error bars represent 95% confidence intervals. *P* values are from the repeated-measures analysis.
Benra=benralizumab; FEV_1=forced expiratory volume in 1 sec; LS=least squares; Q8W=every 8 weeks.
Source: company submission, section B.2.6 figure 17. p. 100

The ERG believe that the analysis of CALIMA data was adequate. Data in this main analysis included also patients with two baseline exacerbations in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations).

Rationale for differences between SIROCCO and CALIMA: regional differences in exacerbation rates

AstraZeneca noted that reductions in exacerbation rates were observed to be greater in the SIROCCO than in the CALIMA trial and suggested that the observation might be due to three key drivers; regional effect, exacerbation history, and background medication.

The CS further suggested that heterogeneity in regional exacerbation rates may have contributed to the size of treatment effect of benralizumab to a greater extent in CALIMA than in SIROCCO. This was supposedly due to the patients from Eastern Europe and South America who were said to have fewer exacerbations in the year before study entry. AstraZeneca also believed that patients who had three or more exacerbations in the previous year before trial were under-represented in the Eastern Europe and South America regions and showed that exacerbation reductions in this subgroup of CALIMA patients were similar to the AER reduction demonstrated in the SIROCCO study (i.e. 51% reduction compared to 57% in SIROCCO). The ERG believe that this explanation may be plausible only if CALIMA had a greater proportion of the study population being composed of patients

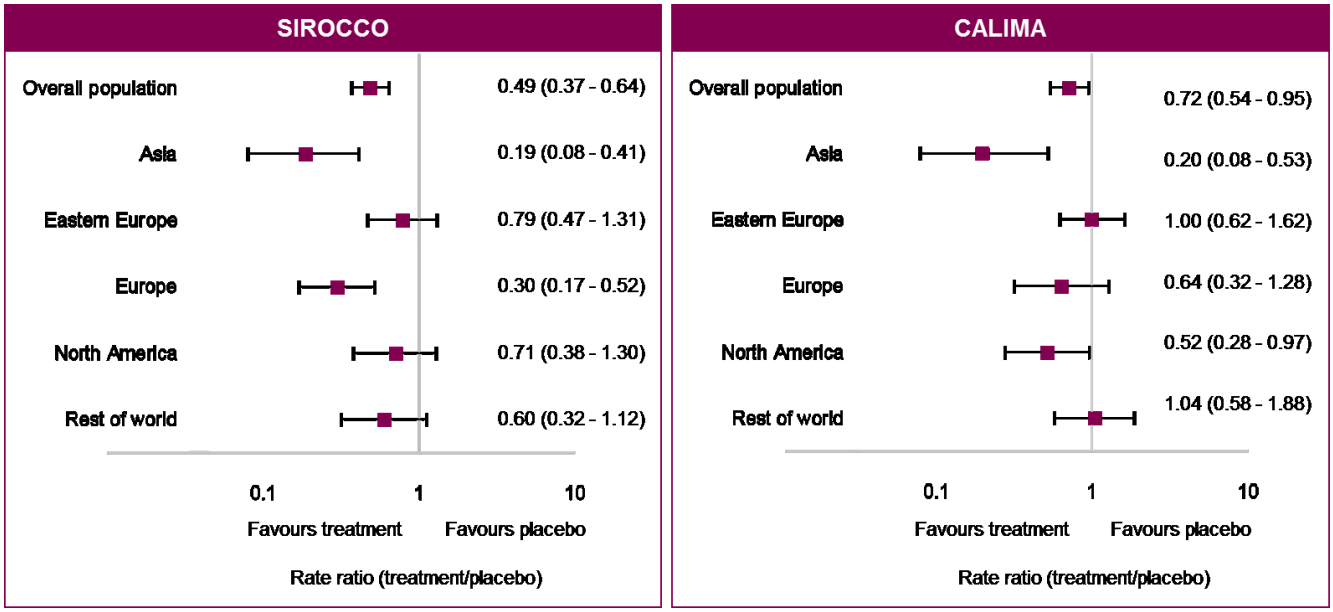
who had very low rates of exacerbations during the preceding year before study compared to the SIROCCO trial. However, the submission showed that the proportion of patients who had ≥ 3 exacerbations in the previous year before the study were similar in CALIMA (39.4%) and SIROCCO (41.4%) Q8W. Also, stratified randomisation was similarly implemented in both trials and would be expected to have ensured this balance.

AstraZeneca also suggested that the efficacy of CALIMA appeared to have been influenced by a strong placebo response because the exacerbation rate of patients in the placebo group during the treatment period of the trial (0.93 per year), was far different from the exacerbation rate of 2.8 seen in the year prior to randomisation. Furthermore, the Sponsor of CALIMA was said to have provided background medication of high dose ICS/LABA to all patients during the entire clinical trial unlike SIROCCO thereby, increasing the potential for a stronger placebo response. The ERG did not believe that this assumption holds true because the difference in exacerbation rates in the year prior to randomisation compared to the study period was quite similar for the placebo groups in CALIMA (1.87) and SIROCCO (1.77). It is likely that the difference in magnitude of treatment effect is related to unknown confounders.

The differences in exacerbation rate reductions, by region, for both SIROCCO and CALIMA is shown in Figure 8. The company noted (source: company submission, section B.2.6, p.100) that;*"……..the hazard ratios for European patients were numerically favourable compared with the overall population. However, analyses of exacerbation rates by region were explanatory and not powered to detect differences, with small n numbers in each group; correspondingly, confidence intervals are wider than the overall population."*

The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both trials only for the Asian population (Figure 8).

Figure 8 Exacerbation rate reduction, by geographical region in SIROCCO and CALIMA analyses (high-dosage ICS/LABA with blood eosinophils ≥300 cells/μL)



Pre-specified subgroup analysis. Values in parentheses represent 95% CIs. Statistical analysis model was a negative binomial mode, including covariates for treatment group, region, use of maintenance OCS, and number of exacerbations in the previous year. Europe encompasses Western Europe and Turkey
Source: company submission, section B.2.6 figure 18, p.102

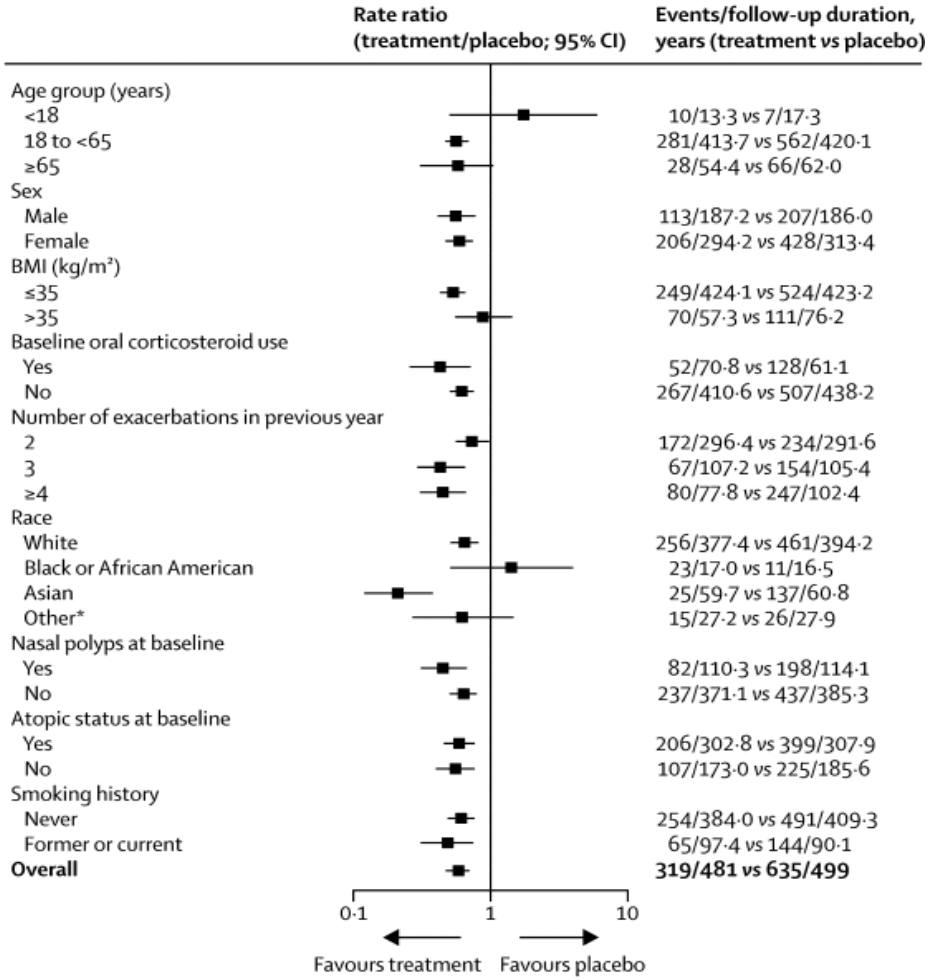
Pooled SIROCCO and CALIMA

The company pooled data from the SIROCCO and CALIMA trials in order to assess the relationship between the clinical efficacy of benralizumab and baseline blood eosinophil counts and exacerbation history, to identify which patients were most likely to benefit from treatment with benralizumab. This pooling was justified by the similar design of the two trials. AstraZeneca also excluded patients on medium-dose ICS in CALIMA trial. The ERG believe that the pooling of the subgroups from the CALIMA and SIROCCO trials was appropriate because randomisation was stratified in both trials, meaning that each of the strata was sufficiently powered and could stand as a separate trial on its own. Data from 1204 patients in SIROCCO and 1091 patients in CALIMA on high-dose ICS plus LABA were pooled to give a total of 2295 patients. In this population, benralizumab Q8W reduced the annual rate of exacerbations by 43% compared with placebo (RR = 0.57; 95% CI: 0.47-0.69, $p < 0.0001$). The ERG believe that a fixed-effects meta-analysis of the summary estimates derived from the analysis of each trial's individual patient data would give the same result as the pooled analysis but a random effects meta-analysis would provide a wider confidence interval.

Subgroup analysis of the pooled data demonstrated that previous exacerbations (Figure 9), baseline blood eosinophil counts (Figure 10), and baseline lung function indices predicted exacerbation reduction. However, the ERG noted that the relationships were not statistically significant as there were overlaps in all 95% CI [34]. FEV_1 change was also predicted by baseline lung function indices (especially FEV_1 reversibility) and eosinophil counts [34]. The data showed higher exacerbation reduction for patients with baseline AER ≥ 3 (Figure 9), and also for patients with baseline blood eosinophil counts ≥ 300 cells/μL (Figure 10) although all 95% CI appeared to overlap.

Benralizumab was found to be more efficacious in patients who had experienced three or more baseline exacerbations compared to patients who experienced two or fewer baseline exacerbations.

Figure 9 Analysis of the effect of patient baseline characteristics on the efficacy of benralizumab treatment



Data are from the ITT population from the high-dosage inhaled corticosteroid treatment cohorts from the SIROCCO and CALIMA studies (baseline blood eosinophils ≥300 cells per μL; full analysis set, pooled). AER was analysed using a negative binomial model.
AER=annual asthma exacerbation rate. BMI=body-mass index. Q8W=every 8 weeks (first three doses every 4 weeks).
Source: company submission, section B.2.6 figure 19, p.103

Figure 10 Annual asthma exacerbation rates by baseline eosinophil count (full analysis set, pooled)

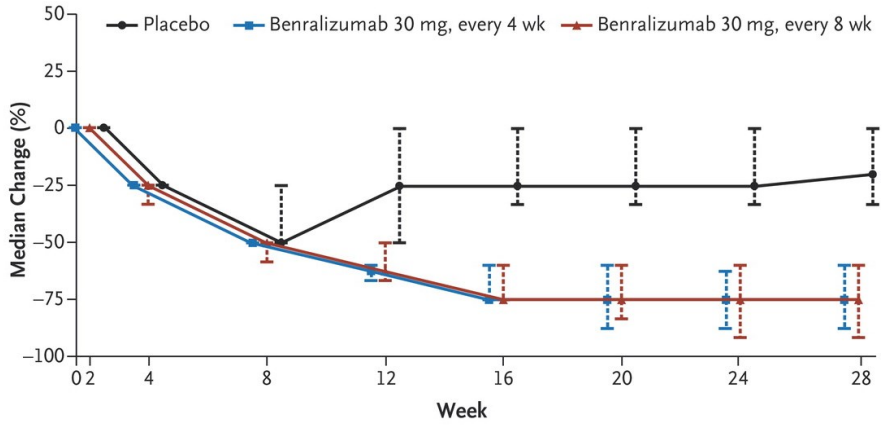
	Placebo (n=777)	Benralizumab Q8W (n=762)
≥0 cells per µL		
Number of patients analysed	770	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·55 to 0·75)
p value *vs* placebo	..	<0·0001
≥150 cells per µL		
Number of patients analysed	648	646
Rate estimate (95% CI)	1·14 (1·02 to 1·28)	0·72 (0·63 to 0·82)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·42 (−0·58 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·63 (0·53 to 0·74)
p value *vs* placebo	..	<0·0001
≥300 cells per µL		
Number of patients analysed	511	499
Rate estimate (95% CI)	1·14 (1·00 to 1·29)	0·65 (0·56 to 0·75)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·49 (−0·67 to −0·32)
Rate ratio *vs* placebo (95% CI)	..	0·57 (0·47 to 0·69)
p value *vs* placebo	..	<0·0001
≥450 cells per µL		
Number of patients analysed	306	298
Rate estimate (95% CI)	1·25 (1·06 to 1·47)	0·62 (0·51 to 0·76)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·63 (−0·87 to −0·39)
Rate ratio *vs* placebo (95% CI)	..	0·50 (0·38 to 0·64)
p value *vs* placebo	..	<0·0001

CI: Confidence interval; Q8W: Every 8 weeks
Source: company submission, section B.2.6 figure 20, p.104

ZONDA

Benralizumab reduced the median final OCS, from baseline OCS, by 75% compared with a 25% reduction in the placebo group ($p < 0.001$) (Figure 11) which translated to a Hodges-Lehman median treatment difference of 37.5% (95% CI 20.8 – 50.0).

Figure 11 Median change from baseline in oral glucocorticoid dose in the ZONDA trial



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

Error bars represent 95% confidence intervals. Values are slightly offset from each other at each time point for clarity.
Source: company submission, section B.2.6 figure 21, p. 104

A greater proportion of patients in benralizumab Q8W had ≥ 90% to 100% reduction from baseline in daily OCS dose at week 28 compared with patients in the placebo group (Table 18). The odds of a reduction in OCS dose according to the CS were 4.12 (95% CI = 2.22-7.63; p < 0.001) times higher with benralizumab than with placebo. The ERG believe that the odds ratio of a reduction in OCS dose appeared to be 3.38 (95% CI = 1.64 – 7.0; p = 0.001) from the data provided, with similar interpretations. Considering the baseline OCS dose, patients on benralizumab receiving ≤ 10mg/d OCS at baseline (n = 38) had a median 100% reduction in OCS dose, compared with a median of 25% for patients in the placebo group (n = 39). About half (52%) of patients who were eligible for a 100% reduction in OCS dose (i.e. those receiving ≤ 12.5mg/d at the end of the run-in phase) achieved the outcome in the benralizumab group, compared with about a fifth (19%) of patients in the placebo group. The CS affirmed that all secondary outcomes regarding the OCS dose were met.

About a quarter (23.3%) of patients on benralizumab experienced an exacerbation compared with about half (52.0%) of patients on placebo over the 28-week treatment period. The AER for patients in the benralizumab Q8W group was 70% lower than for patients in the placebo group (p < 0.001) (Table 18). Change in pre-bronchodilator FEV_1 from baseline was 0.239L in the benralizumab Q8W group compared with 0.126L in the placebo giving a LS mean difference of 0.112L (95% CI; -0.033 to 0. 258) demonstrating some improvement. ACQ-6 score (asthma control) and AQLQ(S)+12 score (asthma-related quality of life) similarly improved from baseline to week 28 (Table 18).

The CS also noted OCS reductions in European patients (Source: company submission, section B.2.6, p. 104) as follows:"Results for OCS reductions in European patients were [redacted] with the overall population, with a mean reduction in OCS dose from baseline of [redacted] for patients receiving benralizumab Q8W (n=22) compared with [redacted] for patients receiving placebo (n=23)."

Table 18 Primary and key secondary outcomes in the ZONDA trial

	Placebo (N=75)	Benralizumab Q8W (N=73)
Primary outcome		
Median OCS dose (range) – mg/day*		
At baseline	10.0 (7.5 – 40.0)	10.0 (7.5 – 40.0)
At final visit	10.0 (0.0 – 40.0)	5.0 (0.0 – 30.0)
Median reduction from baseline (range) - % of baseline value; p value	25.0 (-150 – 100) -	75.0 (-50 – 100) p<0.001
Reduction from baseline in final OCS dose, n (%)		
≥90%	9 (12)	27 (37)
≥70%	15 (20)	37 (51)
≥50%	28 (37)	48 (66)
>0%	40 (53)	58 (79)
Any increase or no change in dose	35 (47)	15 (21)
Analysis of % reduction from baseline in OCS dose		
Odds ratio (95% CI; p value)	-	4.12 (2.22 – 7.63; p<0.001)
Key secondary outcomes		
Final oral glucocorticoid dose of ≤5 mg/day – n (%)		
Odds ratio (95% CI; p value)	-	2.74 (1.41 – 5.31; p=0.002)
Annual asthma exacerbation rate	1.83	0.54
Rate ratio (95% CI; p value)	-	0.30 (0.17 to 0.53; p<0.001)
Pre-bronchodilator FEV1, LS mean change from baseline (L)	0.126	0.239
LS mean difference	-	0.112 L (95% CI, –0.033 to 0.258; p=0.129)
ACQ-6 score change from baseline	–0.57	–1.12
LS mean difference	-	–0.55 (95% CI, –0.86 to –0.23; P=0.001)
AQLQ score from baseline	0.63	1.08
LS mean difference	-	0.45 (95% CI, 0.14 to 0.76; P=0.004)

* The baseline OCS dose was the daily dose at which the patient's asthma was stabilised at randomisation and the final OCS dose was the final daily dose at week 28.

Source: company submission, section B.2.6 table 21, p. 105

4.2.1.1 Subgroup analyses

AstraZeneca suggested that based on the analysis of the SIROCCO and CALIMA trials, benralizumab was found to be more efficacious in patients with blood eosinophils ≥ 300 cells/μL and a history of three or more exacerbations in the previous year compared with patients with lower eosinophil counts and less frequent exacerbations. The ERG believe that the subgroup analyses presented in Figure 9 and Figure 10 included pooled data for all patients enrolled some of whom might not have met the inclusion criteria per NICE scope. Thus, these analyses would appear exploratory. The subgroup analyses provided in the next section appear more relevant to the NICE scope.

The subgroup population provided below for the 259 patients therefore, was a better reflection of the eligible population per NICE scope. However, the drawback is that randomisation was not stratified based also on exacerbation experience in the preceding year before trial entry which makes the analysis more exploratory.

Pooled SIROCCO and CALIMA subgroup analysis

Adult patients with blood eosinophil level ≥ 300 cells/μL and ≥ 3 severe exacerbations, who have failed on high-dose ICS plus LABA therapy

The company pooled 259 patients who met all inclusion criteria per NICE scope from the SIROCCO and CALIMA trials. About a quarter (24%) of patients were on concomitant OCS and 88% were on ICS/LABA. The median time since asthma diagnosis was 16 years (Table 19). Mean number of exacerbation experienced by patients was 4.2 while 24% had experienced exacerbation leading to hospitalisation.

Table 19 Baseline characteristics in the subgroup analysis (pooled SIROCCO and CALIMA)

	Benralizumab 30mg Q8W (N=123)	Placebo (N=136)
Age, mean (SD)	50.8 (11.5)	49.6 (12.7)
Female sex, n (%)	74 (60.2)	93 (68.4)
Race, n (%)		
White	91 (74.0)	106 (77.9)
Black or African American	4 (3.3)	2 (1.5)
Asian	25 (20.3)	21 (15.4)
Other	3 (2.4)	7 (5.1)
Years since asthma diagnosis, median (range)	18.4 (1.3, 66.9)	14.3 (1.2, 69.9)
Pre-bronchodilator FEV_1 (L), mean (SD)	1.60 (0.596)	1.67 (0.632)
Local baseline eosinophil count, mean (SD)	718 (475)	676 (450)
N. exacerbations in past 12 months, mean (SD)	4.0 (1.72)	4.4 (2.32)

N. exacerbations leading to hospitalisation or ER treatment in past 12 months, mean (SD)	0.9 (1.69)	0.9 (1.55)
Patients with ≥1 exacerbations resulting in hospitalisation in past 12 months, n (%)	30 (24.4)	33 (24.3)
Diagnosis of allergic rhinitis, n (%)	77 (62.6)	82 (60.3)
Nasal polyps, n (%)	42 (34.1)	43 (31.6)
History of omalizumab treatment, n (%)	13 (10.6)	16 (11.8)
PRO measures		
Total asthma symptom score	2.84 (1.10)	2.82 (1.01)
ACQ-6 score, mean (SD)	2.87 (0.95)	2.90 (0.92)
AQLQ overall, mean (SD)	3.69 (0.99)	3.87 (0.96)
EQ-5D-5L utility score*	0.73 (0.216)	0.75 (0.181)
Maintenance asthma medication use at baseline		
ICS use, n (%)	123 (100.0)	136 (100.0)
Mean ICS total daily dose (µg)(a)	1236.428	1165.788
LABA use, n (%)	122 (99.2)	136 (100.0)
ICS/LABA use, n (%)	110 (89.4)	117 (86.0)
OCS use, n (%)	29 (23.6)	32 (23.5)
Mean OCS total daily dose (mg)(b)	13.845	12.984
LAMA use, n (%)	20 (16.3)	19 (14.0)
LTRA use, n (%)	62 (50.4)	62 (45.6)
Xanthine derivatives use, n (%)	33 (26.8)	27 (19.9)
Other asthma medications use, n (%)	3 (2.4)	1 (0.7)

(a) ICS doses were converted to their Fluticasone Propionate equivalent for this summary.

(b) OCS doses were converted to their Prednisolone equivalent for this summary.

*UK tariff was used to estimate score

Source: company submission, section B.2.7 table 22, pp.107-108

Clinical effectiveness

Benralizumab demonstrated significant reduction in the annual asthma exacerbation rate by 53% compared with placebo (RR = 0.43, 95% CI: 0.32 – 0.67; p < 001) in the pooled subgroup population, using a negative binomial model. The reduction in AER in the subgroup population is similar to result from the ITT analysis of benralizumab Q8W from the SIROCCO (51%) trial but higher than AER reduction reported for the ITT analysis of benralizumab Q8W from the CALIMA trial (28%). Compared with placebo, benralizumab also reduced the rate of exacerbations associated with ER visits by 69% (p = 0.051), improved pre-bronchodilator FEV_1 by 254ml (p < 0.001) and PRO scores of ACQ-6 (asthma control) and EQ-5D-5L (quality of life) from baseline (Table 20). However, improvements in asthma control did not reach MCID. Change in asthma-related quality of life exacerbations

associated with hospitalisation were similar between benralizumab and placebo, although event rates were low.

Table 20 Efficacy in the pooled SIROCCO and CALIMA subgroup analysis

Estimate, 95% CI	Benralizumab 30mg Q8W (N=123)	Placebo (N=136)
Marginal annual exacerbation rate	0.85 (0.63, 1.15)	1.83 (1.45, 2.30)
Marginal absolute difference	-0.98 (-1.46, -0.50)	
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)
Marginal absolute difference	-0.10 (-0.22, 0.01)	
Rate ratio	0.31 (0.09, 1.01)	
P value	0.051	
Annual exacerbation rate associated with hospitalisation	Not calculated*	Not calculated*
Rate ratio	1.01 (0.30, 3.45)	
P value	0.988	
FEV_1 pre-bronchodilator change from baseline (L)	0.485	0.231
Estimate for difference	0.254 (0.113, 0.395)	
P value	<0.001	
ACQ-6 score change from baseline	-1.59	-1.16
Estimate for difference	-0.43 (-0.69, -0.16)	
P value	0.002	
Mean EQ-5D-5L score change from baseline	0.10 (0.08, 0.13)	0.06 (0.04, 0.09)
Estimate for difference	0.04 (0.01, 0.08)	
P value	0.019	

* The crude rate was 0.09 for benralizumab and 0.14 for placebo
Source: company submission, section B.2.7 table 23, p. 109

ZONDA

[redacted]

[redacted]

21

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	

[redacted]

Source: company submission, section B.2.7 table 24, p. 110

Mortality in pivotal trials

[redacted]

4.2.2 Safety of benralizumab

4.2.2.1 Overall Rates of AEs

Across all three pivotal trials, the rates of AEs and serious AEs were numerically lower for benralizumab Q8W compared with placebo. Rates of experiencing any AE ranged from 68% to 75% for patients receiving benralizumab across the trials, and from 76% to 83% for patients receiving placebo. Rates of serious AEs ranged from 9% to 13% for benralizumab and from 14% to 19% for placebo. The ERG noted that this safety profile was based on short-term trial data (maximum 12 months duration) which included patients treated with a maintaining oral corticosteroid dose (16.3% patients in SIROCCO trial; 9.3% patients in CALIMA trial; 100% patients in ZONDA trial).

The most commonly experienced AEs across the trials consistently included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis. Hypersensitivity reactions were infrequent and similar between arms. Relative risk calculations did not indicate an increased risk of any specific AEs when compared between all three trials.

A summary of AEs experienced in SIROCCO, CALIMA, and ZONDA is presented in Table 22, Table 23 and Table 24 respectively. The CS points out that these studies were not powered to detect differences in event rates of AEs, and states these calculations to be exploratory.

Table 22 Summary of AEs experienced in SIROCCO

	Placebo (n=407)	Benralizumab 30 mg Q8W (n=394)	Risk difference	Relative risk (95% CI)
Any adverse event	311 (76%)	281 (71%)	-5.1%	0.93 (0.86 - 1.01)
Any adverse event leading to treatment discontinuation	3 (<1%)	8 (2%)[‡]	1.3%	2.75 (0.74 - 10.31)
Any serious adverse event	55 (14%)	52 (13%)	-0.3%	0.98 (0.69 - 1.39)
Deaths	2 (1%)	1 (<1%)	-0.2%	0.52 (0.05 - 5.67)
Adverse events in >3% of patients[‡]				
Asthma	78 (19%)	45 (11%)	-7.7%	0.60 (0.42 - 0.84)
Nasopharyngitis	47 (12%)	46 (12%)	0.1%	1.01 (0.69 - 1.48)
Upper respiratory tract infection	36 (9%)	32 (8%)	-0.7%	0.92 (0.58 - 1.45)
Headache	21 (5%)	37 (9%)	4.2%	1.82 (1.09 - 3.05)
Bronchitis	30 (7%)	19 (5%)	-2.5%	0.65 (0.37 - 1.14)
Sinusitis	28 (7%)	22 (6%)	-1.3%	0.81 (0.47 - 1.39)
Influenza	23 (6%)	19 (5%)	-0.8%	0.85 (0.47 - 1.54)
Pharyngitis	14 (3%)	23 (6%)	2.4%	1.70 (0.89 - 3.25)

Rhinitis	15 (4%)	10 (3%)	-1.1%	0.69 (0.31 - 1.51)
Arthralgia	10 (2%)	18 (5%)	2.1%	1.86 (0.87 - 3.98)
Cough	10 (2%)	13 (3%)	0.8%	1.34 (0.60 - 3.03)
Pyrexia	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Back pain	15 (4%)	8 (2%)	-1.7%	0.55 (0.24 - 1.28)
Acute sinusitis	10 (2%)	13 (3%)	0.8%	1.34 (0.60 - 3.03)
Rhinitis allergic	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Nausea	8 (2%)	12 (3%)	1.1%	1.55 (0.64 - 3.75)
Gastroenteritis	6 (1%)	12 (3%)	1.6%	2.07 (0.78 - 5.45)
Pain in extremity	5 (1%)	13 (3%)	2.1%	2.69 (0.97 - 7.46)
Injection-site reactions	8 (2%)	9 (2%)	0.3%	1.16 (0.45 - 2.98)
Hypersensitivity adverse events§	11 (3%)	11 (3%)	0.1%	1.03 (0.45 - 2.36)
Causally related¶	2 (<1%)	2 (<1%)	0	1.03 (0.15 - 7.30)
Urticaria	2 (<1%)	2 (<1%)	0	1.03 (0.15 - 7.30)

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end-of-treatment visit. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

* Includes four patients in the Q8W cohort who received extra doses of benralizumab.

† One additional patient discontinued the study after receiving their last dose but before attending the end-of-treatment visit.

‡ Medical Dictionary for Regulatory Activities version 18.1.

§ High-level term.

¶ In the opinion of the investigator.

Source: company submission section B.2.10 table 31, pp. 127-128

Table 23 Summary of AEs experienced in CALIMA

	Placebo (n=440)	Benralizumab 30 mg Q8W (n=428)	Risk difference	Relative risk (95% CI)
Any adverse event	342 (78%)	320 (75%)	-3.0%	0.96 (0.89 - 1.04)
Any drug-related adverse event	36 (8%)	54 (13%)	4.4%	1.54 (1.03 - 2.30)
Any adverse event leading to treatment discontinuation	4 (<1%)	10 (2%)	1.4%	2.57 (0.81 - 8.13)
Any adverse event leading to death	0	2 (<1%)	0.5%	5.14 (0.25 106.75)
Any serious adverse event	60 (14%)	40 (9%)	-4.3%	0.69 (0.47 - 1.00)
Adverse event in >3% of patients*				
Nasopharyngitis	92 (21%)	79 (18%)	-2.6%	0.88 (0.67 - 1.16)
Asthma	68 (15%)	47 (11%)	-4.8%	0.71 (0.50 - 1.01)
Bronchitis	52 (12%)	44 (10%)	-1.6%	0.87 (0.60 - 1.27)
Upper respiratory tract infection	41 (9%)	36 (8%)	-0.9%	0.90 (0.59 - 1.38)
Headache	32 (7%)	34 (8%)	0.8%	1.09 (0.69 - 1.74)
Sinusitis	37 (8%)	20 (5%)	-4.0%	0.56 (0.33 - 0.94)
Influenza	24 (5%)	14 (3%)	-2.3%	0.60 (0.31 - 1.14)

Rhinitis allergic	23 (5%)	16 (4%)	-1.6%	0.72 (0.38 - 1.33)
Hypertension	21 (5%)	18 (4%)	-0.6%	0.88 (0.48 - 1.63)
Rhinitis	17 (4%)	17 (4%)	0.1%	1.03 (0.53 - 1.99)
Back pain	16 (4%)	11 (3%)	-1.1%	0.71 (0.33 - 1.51)
Acute sinusitis	14 (3%)	5 (1%)	-2.2%	0.37 (0.13 - 1.01)
Arthralgia	9 (2%)	14 (3%)	1.3%	1.60 (0.70 - 3.66)
Cough	8 (2%)	14 (3%)	1.6%	1.80 (0.76 - 4.24)
Pharyngitis	7 (2%)	10 (2%)	0.8%	1.47 (0.56 - 3.82)
Pyrexia	6 (1%)	12 (3%)	1.6%	2.06 (0.78 - 5.43)
Injection-site reactions	8 (2%)	9 (2%)	0.3%	1.16 (0.45 - 2.97)
Hypersensitivity	17 (4%)	13 (3%)	-0.9%	0.79 (0.39 - 1.60)
Drug-related hypersensitivity	2 (<1%)	4 (<1%)	0.5%	2.06 (0.38 - 11.17)

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end of therapy visit. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

* Medical Dictionary for Regulatory Activities version 18.1.

Source: company submission section B.2.10 table 32, pp. 128-129

Table 24 Summary of AEs experienced in ZONDA

	Placebo (n=75)	Benralizumab 30 mg Q8W (n=73)	Risk difference	Relative risk (95% CI)
Any adverse event	62 (83)	55 (75)	-7.3%	0.91 (0.77 - 1.08)
Any adverse event leading to treatment discontinuation	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Any adverse event leading to death	0	2 (3)	2.7%	5.13 (0.25 - 105.17)
Any serious adverse event	14 (19)	7 (10)	-9.1%	0.51 (0.22 - 1.20)
Adverse event in ≥3% of patients*				
Nasopharyngitis	15 (20)	11 (15)	-4.9%	0.75 (0.37 - 1.53)
Bronchitis	12 (16)	7 (10)	-6.4%	0.60 (0.25 - 1.44)
Headache	4 (5)	6 (8)	2.9%	1.54 (0.45 - 5.24)
Rhinitis	2 (3)	6 (8)	5.6%	3.08 (0.64 - 14.78)
Upper respiratory tract infection	5 (7)	5 (7)	0.2%	1.03 (0.31 - 3.40)
Sinusitis	8 (11)	4 (5)	-5.2%	0.51 (0.16 - 1.63)
Asthma	18 (24)	2 (3)	-21.3%	0.11 (0.03 - 0.47)
Influenza	5 (7)	1 (1)	-5.3%	0.21 (0.02 - 1.72)
Hypertension	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Pneumonia	3 (4)	3 (4)	0.1%	1.03 (0.21 - 4.93)
Vertigo	2 (3)	3 (4)	1.4%	1.54 (0.27 - 8.96)
Presyncope	0	3 (4)	4.1%	7.19 (0.38 - 136.79)
Back pain	4 (5)	2 (3)	-2.6%	0.51 (0.10 - 2.72)

Cough	4 (5)	1 (1)	-4.0%	0.26 (0.03 - 2.24)
Dyspnoea	4 (5)	1 (1)	-4.0%	0.26 (0.03 - 2.24)
Nausea	3 (4)	0	-4.0%	0.15 (0.01 - 2.79)
Oral candidiasis	4 (5)	0	-5.3%	0.11 (0.01 - 2.09)
Status asthmaticus	3 (4)	0	-4.0%	0.15 (0.01 - 2.79)
Injection-site reaction	2 (3)	0	-2.7%	0.21 (0.01 - 4.21)
Hypersensitivity	1 (1)	2 (3)	1.4%	2.05 (0.19 - 22.17)
Urticaria	1 (1)	1 (1)	0.0%	1.03 (0.07 - 16.12)

Data are number of patients (%).

* Medical Dictionary for Regulatory Activities version 18.1.

Source: company submission section B.2.10 table 33, pp.129-130

4.2.2.2 AEs of special interest

4.2.2.3 Serious adverse events (SAEs) and drug-related AEs

There were higher incidences of related TEAEs being reported by patients in both the benralizumab groups (30 mg 4W; 30mg 8W) versus placebo. The majority of TEAEs were assessed as not related to benralizumab. Most common drug-related AEs were headache, pyrexia and fatigue. However, the incidence of all TEAEs that were of severe intensity were similar across groups. The most common severe intensity TEAEs were asthma and pneumonia.

4.2.2.4 AEs leading to withdrawal from treatment

A numerically higher proportion of patients receiving benralizumab discontinued treatment due to an AE (21 patients receiving benralizumab, compared with 9 patients receiving placebo in total), although the CS stated that no trends in specific adverse events leading to discontinuation were observed. The company responded to ERG's clarification questions by stating that adverse events that led to treatment discontinuation were slightly more frequent in the benralizumab Q8W and Q4W groups (2%) than in the placebo groups (<1%) in both the SIROCCO and CALIMA studies; these events mostly involved single patients and were distributed across multiple system organ classes without an apparent pattern. Adverse events that led to treatment discontinuation in the ZONDA study were generally balanced between the benralizumab and placebo groups and without apparent pattern.

- In SIROCCO, urticaria and arthralgia were the only TEAEs leading to discontinuation of investigational product in more than one patient (2 patients [0.5%] each in the benralizumab 30 mg Q8W group)

- In CALIMA, asthma was the only TEAE leading to discontinuation of investigational product in more than one patient (2 patients [0.5%] in the benralizumab 30 mg Q8W group and 1 patient [0.2%] in the placebo group
- In ZONDA, there were no AEs leading to discontinuation of investigational product in more than one patient

4.2.2.5 AEs in the subgroup analysis

In the pooled SIROCCO and CALIMA subgroup analysis (for patients inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl AND ≥3 prior asthma exacerbations), 80.5% of patients who received benralizumab experienced an AE (99/123), compared with 81.6% of patients who received placebo (111/136). The rate of serious AEs was 17.9% in the benralizumab group and 11.8% in the placebo group, while the rate of AEs leading to discontinuation of treatment was 4.1% versus 0.7%, respectively. Serious AEs and discontinuations were examined between the groups and the CS states that AEs were spread across many different systems, with no trend for any particular system to be affected.

[redacted] However, the ERG noted in the CSR [redacted]).

4.2.2.6 Deaths and long-term safety

The incidence of deaths was low. In the pooled CALIMA – SIROCCO subgroup analysis (for patients inadequately controlled, despite high-dose ICS plus LABA, with blood EOS count ≥300 cells per µl AND ≥3 prior asthma exacerbations), the CS state that one patient in the benralizumab arm died due to AEs (overdose), which was not considered to be study drug-related.

[redacted]. However, the ERG noted that the ZONDA CSR reported [redacted]

[redacted]25

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

The CS reported no malignancy events in the short-term (one year) in any of the three key trials. There were no events of anaphylactic reaction causally related to benralizumab, and the ERG noted that patients were excluded from SIROCCO and CALIMA study if they had a history of anaphylaxis with any biologic drug.

The ERG requested additional data on risk of relapse following discontinuation with benralizumab. AstraZeneca responded by saying no formal studies had been conducted to assess withdrawal or rebound effects and that there had been very little opportunity for real world use of benralizumab with which to generate additional safety and efficacy data.

4.2.2.7 Summary of safety data

The CS stated that in terms of safety outcomes, benralizumab was found to be well tolerated, with rates of AEs, serious AEs, and AEs leading to discontinuation of treatment being similar between benralizumab and placebo. The ERG noted that this safety profile was based on short-term trial data (maximum 12 months duration) which included patients treated with a maintaining oral corticosteroid dose (16.3% patients in SIROCCO trial; 9.3% patients in CALIMA trial; 100% patients in ZONDA trial). Patients in all three studies had the opportunity to continue open label treatment with benralizumab in the longer-term safety extension study called BORA, the results of which were not yet available. However, the ERG noted that there had been very little opportunity for real world use of benralizumab with which to generate additional safety and efficacy data.

Most AEs observed in the trial were mild to moderate in intensity, and not considered to be related to treatment. The most commonly experienced AEs across the trials consistently included worsening asthma, nasopharyngitis, upper respiratory tract infection, headache,

and bronchitis. Small numerical differences in incidences were observed across groups for some of the most common TEAEs, notably headache, pyrexia and fatigue, although none of these differences were considered by the CS to be clinically meaningful.

The CS stated that no deaths were considered to be related to treatment. However, the ERG noted in the CSR

[redacted]

Adverse events that led to treatment discontinuation were slightly more frequent in the benralizumab Q8W and Q4W groups (2%) than in the placebo groups (<1%) in both the SIROCCO and CALIMA studies. TEAEs leading to discontinuation were urticaria and arthralgia (SIROCCO), and asthma (CALIMA).

Study durations ranged from 28 weeks (ZONDA) to 48 weeks (SIROCCO), to 56 weeks (CALIMA), and longer-term data needed to confirm the persistence of treatment effect are not currently available. The ongoing BORA and MELTEMI extension trials are designed to evaluate long-term efficacy and safety with benralizumab (CS Section B.2.11).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Search strategy for indirect treatment comparison

The CS reported that a systematic literature review (SLR) was undertaken and that it was conducted "in accordance with NICE guidance, and the University of York CRD standards and Cochrane standards" (CS Section B.2.9, p.112). A critique of the clinical effectiveness searches was presented in Section 4.1 of the ERG's report above. The clinical effectiveness searches were reasonably well conducted and reported, although a few concerns regarding the searches were identified by the ERG. These were also listed below in brief for clarity:

- The filter used to limit to RCTs was an 'adapted' version of the SIGN (Scottish Intercollegiate Guidelines Network) RCT filter. It was unclear why it was necessary to alter this validated filter, or why a validated search filter was not used to limit to RCTs.
- The proprietary drug name 'Fasenra' was not included in the search terms, although proprietary drug names for comparator drugs were included.
- The ERG did not have access to Embase.com so was unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy

was debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).

4.3.2 Assessment of the feasibility of conducting network meta-analysis

Initially, the CS considered conducting a network meta-analysis (NMA) to simultaneously compare relevant interventions and comparators (CS Section B.2.9, pp.113-114). Heterogeneity is an important consideration in NMA [35]. AstraZeneca identified key reasons among the ten studies potentially eligible for NMA to consider NMA unsuitable in this instance.

In summary,

- Eight studies considered adolescents from age 12, whereas two studies included adults from age 18
- Two studies recruited patients receiving ICS irrespective of whether or not they were receiving an additional controller, whereas the remainder required at least one additional controller
- Of the six studies that recruited patients receiving high-dose ICS plus at least one additional controller, two studies did not define 'high-dose', two used a cut-off of >500 µg FP daily or equivalent and two used a cut-off of ≥880 µg FP daily or equivalent
- Two studies had no criteria regarding exacerbation history, three studies required patients to have had ≥1 exacerbation in the past year, while five studies required patients to have had ≥2 exacerbations in the past year
- Eight studies implemented an inclusion criterion regarding blood eosinophil count, and five different thresholds were used
- The proportion of patients using maintenance OCS at baseline ranged from 9% to 100%

There were also a number of specific differences between the benralizumab trials and trials of mepolizumab and reslizumab (CS Section D1.2, pp.337-338). Therefore, the ERG agreed with AstraZeneca's decision not to conduct NMA.

4.3.3 Study selection criteria for indirect treatment comparison

Based on the NICE DSU recommendations [36], AstraZeneca proposed matched-adjusted indirect comparisons (MAIC) as the method for indirect treatment comparisons. Since NMA was not considered feasible, the CS reported that MAIC was selected as the method for indirect comparison. From studies identified by the SLR, a specific set of criteria were

applied to determine eligibility for the MAIC analysis. Table 26 delineates these inclusion criteria:

Table 26 Summary of objectives and eligibility criteria for the MAIC

Objectives	
Objectives	To compare benralizumab against other launched respiratory biologics, i.e. mepolizumab and reslizumab, in patients with severe asthma uncontrolled on high-dose ICS plus LABA (medium- to high-dose ICS plus LABA when compared with reslizumab), and ideally in mepolizumab and reslizumab NICE-recommended populations, respectively
Eligibility criteria	
Population	• Age: adults and adolescents (≥12 years) • Gender: any • Race: any • Disease: severe asthma that is uncontrolled despite treatment with high-dose ICS plus at least one additional controller (medium- to high-dose ICS when compared with reslizumab)
Interventions	Approved biologics • Benralizumab • Mepolizumab • Reslizumab Only studies evaluating approved/labelled doses of interventions were included in the MAIC
Comparators	• Placebo/best supportive care • Medium or high-dose ICS + at least one additional controller. • Medium-dose ICS + 1 additional controller (e.g., LABA/LTRA/LAMA/theophylline) • High-dose ICS + 1 additional controller (e.g. LABA/LTRA/LAMA/theophylline) • High-dose ICS + 2 additional controllers (e.g., LABA + LAMA/LABA+LTRA) • High-dose ICS + at least one additional controller + OCS maintenance treatment
Study designs	• RCTs • Phase III • Phase II trials were not considered for analysis being exploratory in nature and do not provide a definitive answer regarding the clinical benefit of the intervention in question • In addition, studies not powered to detect differences in efficacy outcomes were not considered in the analysis
Language	English language studies
Publication timeframe	Database inception to 17 October 2017 Conference proceedings for past 3 years (searched on 17 October 2017)

ICS: Inhaled corticosteroid; LABA: Long-acting beta-2 agonist; MAIC: Matching-adjusted Indirect Comparison; OCS: oral corticosteroid; RCT: Randomised controlled trial
Source: company submission section B.2.9 table 28, pp.117-118

AstraZeneca included adolescents aged 12 upwards in the MAIC, whereas the NICE scope stated that the appraisal should consider adults. BTS/SIGN guidelines for asthma state that the "signs and symptoms of asthma in adolescents" are no different than those of adult asthma. Clinical advisor to the ERG, David Halpin, also considered that the inclusion of adolescents would not make a substantial difference. In response to a question from the ERG about the age range (ERG's clarification question, A7), AstraZeneca stated (Company response to clarification question, A7) that adolescents constituted a small proportion (<5% in all cases) of participants in both benralizumab and mepolizumab trials were adolescents, and that "there were no differences in the results after removing adolescent patients", although results were not provided for the ERG to scrutinise. The ERG was satisfied that the divergence from the NICE scope with regard to age range was minor and made no material difference to the results of the included analyses.

The ERG noted the exclusion of phase II RCTs from AstraZeneca's evidence submission and did not consider this to be particularly standard practice. For example, the submission for the NICE mepolizumab appraisal considered all RCTs, as well as observational studies, for both efficacy and safety outcomes. AstraZeneca did not provide scenario analyses to explore whether the MAIC results would change if phase II RCTs were included.

4.3.4 Decision not to conduct MAIC for the comparison between benralizumab and reslizumab

AstraZeneca deemed the data to be unsuitable to conduct a MAIC analysis comparing benralizumab and reslizumab. AstraZeneca admitted that there were "key differences within the two trial populations in terms of baseline characteristics" (CS Section B.3.3, p.162-163) for both the comparison between benralizumab and mepolizumab, and the comparison between benralizumab and reslizumab. AstraZeneca stated that MAIC would be the most robust method of comparing benralizumab and reslizumab (CS Section B.3.3, p.163). However, in the case of benralizumab and reslizumab, the nature of the differences between the trial populations for the two technologies meant that the available effective sample size for this comparison was reduced to 20 (CS Section B.3.3., p.163). However, it should be noted that the ERG was not provided with IPD and could not verify the accuracy of this effective sample size. Additionally, the CS stated that there was a highly skewed distribution of weights, which the ERG agreed would indicate a lack of population overlap and be problematic for MAIC analysis. The ERG agreed with AstraZeneca that a MAIC analysis comparing these technologies appeared unfeasible.

The key clinical features of the benralizumab and reslizumab trials are compared in the following tables:

Table 27 Summary of study characteristics of the benralizumab and reslizumab studies

Study	SIROCCO	CALIMA	Study 3082	Study 3083
Interventions	Benralizumab 30 mg Q8w		Reslizumab 3.0 mg/kg	
	Placebo		Placebo	
Phase	III		III	
Sample size	805	881	489	464
Method of randomisation	Adequate	Adequate	Adequate	Adequate
Blinding status	Double-blind	Double-blind	Double-blind	Double-blind
Study duration	48 weeks	64 weeks	65 weeks	65 weeks
Treatment duration	48 weeks	56 weeks	52 weeks	52 weeks
Primary outcome	Annual rate ratio versus placebo of asthma exacerbations for patients receiving high-dosage ICS plus LABA with baseline blood EOS ≥300 cells/Ml		The primary endpoint was the frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee.	
Secondary outcomes	• ACQ-5 responders • ACQ-5 score • ACQ-6 responders • ACQ-6 scores • Annual rate of asthma exacerbations requiring ED visit, urgent care visit, or hospitalisation • AQLQ(S)+12 score • Blood EOS count • EQ-5D scores	• ACQ-5 responders • ACQ-5 score • ACQ-6 responders • ACQ-6 scores • Annual rate of asthma exacerbations requiring ED visit, urgent care visit, or hospitalisation • AQLQ(S)+12 score • Blood EOS count • EQ-5D scores	• Change in FEV1 from baseline over 16 weeks • ACQ-7 score • ASUI score, • Rescue use of short-acting β-agonist • Blood EOS count to each scheduled visit • AQLQ total score	

	• Global impression of change • Morning and evening PEFR • Nights with nocturnal awakening due to asthma and requiring rescue medication • Post-bronchodilator FEV1 • Pre-bronchodilator FEV1 • Rescue medication use • Time to first clinically significant asthma exacerbation • Time to first exacerbation requiring hospitalisation or ED visit • Total days of exacerbations requiring systemic corticosteroids • Total asthma symptom score for patients receiving high-dosage ICS plus LABA with baseline blood EOS count ≥300 cells/µL • Safety	• Global impression of change • Morning and evening PEFR • Nights with nocturnal awakening due to asthma and requiring rescue medication • Post-bronchodilator FEV1 • Pre-bronchodilator FEV1 • Rescue medication use • Time to first asthma exacerbation • Time to first exacerbation requiring hospitalisation or ED visit • Total days of exacerbations requiring systemic corticosteroids • Total asthma symptom score for patients receiving high-dosage ICS plus LABA with baseline blood EOS count ≥300 cells/µL • Safety	

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life; ASUI: Asthma Symptom Utility Index; BENRA: Benralizumab; CSR: Clinical Study Report; ED: Emergency Department; EOS: Eosinophil; FEV1: Forced Expiratory Volume in one Second; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; LABA: Long-acting beta-2 agonist; MEPO: Mepolizumab; NO: Nitric oxide; OCS: Oral corticosteroid; PEF: Peak Expiratory Flow; SD: Standard Deviation; SGRQ: St. George Respiratory Questionnaire; Q8W: every eight weeks

Source: company submission, section D.1.2 table 173, pp. 393-394.

Table 28 Comparison of inclusion/exclusion criteria in the benralizumab and reslizumab studies

Characteristics	SIROCCO	CALIMA	Study 3082	Study 3083
Age	12-75 years		12-75 years	
Disease severity	Severe uncontrolled asthma		Moderate to severe uncontrolled asthma	
Baseline medication for asthma	High-dose ICS (adults: >500 µg of FP or equivalent) + LABA ± OCS or any other controller	Medium (>250 to 500 µg of FP or equivalent) to high-dose ICS (>500 µg of FP or equivalent) + LABA ± OCS or any other controller	At least a medium-dose ICS (≥440 µg FP per day, or equivalent) ± other controller drug (including OCS)	
Exacerbation history	≥2 exacerbations in the past year requiring systemic corticosteroid use or temporary increase in the patient's usual maintenance OCS dosage		≥1 exacerbation that needed a systemic corticosteroid within the past 12 months	
Eosinophilic asthma	No restriction		≥400 cells/µL during a 2-4 week screening period	

Highlighted cells indicate differences across benralizumab and reslizumab studies
FP: Fluticasone propionate; ICS: Inhaled corticosteroid; LABA; Long-acting beta-2 agonist; OCS; Oral corticosteroid
Source: company submission, section D.1.2 table 174, p.395.

Table 29 Overview of baseline characteristics as reported in the benralizumab and reslizumab studies

Characteristics	SIROCCO	CALIMA	Study 3082	Study 3083	Study 3082 and 3083 (Pooled)
Population	**Overall**	**Overall**	**Overall**	**Overall**	**Overall**

Characteristics	SIROCCO		CALIMA		Study 3082		Study 3083		Study 3082 and 3083 (Pooled)	
	High-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS		Medium- to high-dose ICS	
	BENRA Q8W, N=398	Placebo, N=407	BENRA Q8W, N=441	Placebo, N=440	RESLI 3 mg/kg, N=245	Placebo, N=244	RESLI 3 mg/kg, N=232	Placebo, N=232	RESLI 3 mg/kg, N=477	Placebo, N=476
Age, years	47.6	48.7	49.0	48.8	46.6*	46.7*	46.4*	47.5*	-	-
Gender (% males)	36.7	33.9	38.1	40.0	42.0	34.0	38.0	35.0	40.04	34.45
BMI	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.7 (6.3)	28 (6.2)	27 (5.1)	27 (5.3)	-	-
FEV1 predicted (%)	56.1$	56.6$	57.9	58.0	63.6	65.0	70.4	68.0	-	-
Reversibility (%)	27.2	25.5	24.6	27.3	26.1	26.3	28.1	28.7	-	-
ACQ scores**	2.8	2.87	2.82	2.73	2.66	2.76	2.57	2.61	-	-
Never smokers (% patients)	82.2	80.6	78.9	79.3	-	-	-	-	-	-
OCS use (% patients)	17.8	16.2	10.0	8.9	19.0	19.0	12.0	12.0	-	-
Mean EOS count (cells/µl)	469.8	456.5	465.1	487.5	696.0	624.0	610.0	688.0	-	-
Exacerbation in previous year, mean	2.8	3	2.7	2.8	1.9	2.1	1.9	2.0	-	-
1 exacerbation in previous year	0.0	0.0	0.2	0.0	-	-	-	-	58.07	59.24
2 exacerbations in previous year	63.3	60.0	65.1	65.5	-	-	-	-	18.03	22.48

Characteristics	SIROCCO		CALIMA		Study 3082		Study 3083		Study 3082 and 3083 (Pooled)	
≥3 exacerbations in previous year	19.8	18.7	21.1	21.1	-	-	-	-	9.22	7.56
≥4 exacerbations in previous year	16.9	21.3	13.6	13.4	-	-	-	-	14.05	10.08
Omalizumab use (% patients)	7.0	7.6	2.7	3.8	-	-	-	-	-	-
Nasal polyps (% patients)	23.2	23.2	16.8	18.1	-	-	-	-	-	-

Highlighted cells indicate differences across benralizumab and reslizumab studies. $Data are extracted from respective publications. All other values for BENRA trials are extracted from respective CSRs.*Extracted from RESLI NICE STA; All other data for RESLI trials are extracted from respective publications. **ACQ-5 in BENRA trials and ACQ-7 in RESLI trials.
ACQ; Asthma Control Questionnaire; BENRA: Benralizumab; BMI; Body Mass Index; CSR; Clinical study report; EOS: Eosinophil; FEV1: Forced Expiratory Volume in one second; ICS; Inhaled Corticosteroid; NICE: National Institute for Health and Care Excellence; OCS: Oral corticosteroid; RESLI: Reslizumab; STA: Single Technology Appraisal; Q8W: every eight weeks
Source: company submission, section D.1.2 table 175, pp.396-397

Table 30 Definition of clinically significant exacerbations reported across the studies

Outcome	Study name	Outcome definition
Clinically significant exacerbations	SIROCCO	An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable OCS background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) visit to an ED or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥24 h) because of asthma
	CALIMA	An asthma exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids; (2) visit to an ED or urgent care visit (<24 h) due to asthma that required systemic corticosteroids; or (3) an inpatient admission to hospital (≥24 h) due to asthma
	Study 3082 and Study 3083	Clinical asthma exacerbations were defined as worsening of asthma that resulted in use of systemic corticosteroids in patients not already receiving treatment, or a two-times increase in the dose of either ICS or systemic corticosteroids for 3 or more days, or the need for asthma-related emergency treatment (ER visit, hospital admission, or unscheduled physician's office visit for nebuliser or other urgent treatment).

ED: Emergency department; ER: Emergency room; ICS: Inhaled corticosteroid; OCS: Oral corticosteroid
Source: company submission, Section D.1.2 table 176, p.39

However, AstraZeneca then assumed that "all clinical values, and therefore transition probabilities are equivalent between the two products" (CS Section 3.3.2.3, p.178). Clinical advisor to the ERG, David Halpin, considered that this assumption may not be valid in light of differing mechanisms of action. The CS on several occasions stressed how benralizumab was not comparable to mepolizumab or reslizumab in terms of mechanism of action, so while extrapolating between mepolizumab and reslizumab may be justifiable in light of similarity of mechanism of action, extrapolating between one of these and benralizumab was unjustified. The CS, for example, stated that benralizumab "has an innovative and unique mechanism of action. By binding to eosinophils through IL-5Rα, benralizumab blocks the binding of the IL-5 ligand to its receptor, and inhibits the activity of IL-5 and the subsequent activation of the eosinophil" (CS Section B.2.12, p.133). The potential effects of this invalid extrapolation were unknown, but could bias the model results comparing benralizumab with reslizumab.

The ERG asked AstraZeneca to provide further justification for their decision (ERG's clarification question, A8). In their response (Company response to clarification question, A8), AstraZeneca stated that "in the absence of head-to-head data or a feasible indirect comparison, we compared baseline characteristics and ITT results between the benralizumab and reslizumab studies." The ERG agreed that there did not appear to be a

feasible indirect comparison between benralizumab and reslizumab. However, the results that they provided did not appear to support the notion of clinical equivalency. For example, they stated that "patients in the reslizumab studies had lower baseline exacerbation rates, but higher baseline eosinophil levels than in the benralizumab studies…Other key differences included the use of ACQ measures; benralizumab trials reported ACQ-6, while reslizumab trials reported ACQ-7." The response also stated: "The annual rate ratio for clinical asthma exacerbation reductions was 0.50 (0.37-0.67) in Study 1 and 0.41 (0.28-0.59) in Study 2 for RES versus placebo. This is comparable to the exacerbation reductions rate ratio for SIROCCO of 0.49 (95% CI: 0.37 - 0.64). The rate ratio for CALIMA was less favourable than SIROCCO (RR: 0.72; 95% CI: 0.54 - 0.95); however, this can be explained by regional differences in exacerbation rates at baseline, a strong placebo response, and background medication (see page 99 of the main submission)."

With regard to mechanism of action, building on discussion in the CS regarding the uniqueness of benralizumab, AstraZeneca's response admitted these differences are marked, saying that "benralizumab leads to rapid and near complete depletion of eosinophils and basophils through ADCC (anti-body dependent cell-mediated cytotoxicity), while mepolizumab and reslizumab act through the indirect mechanism of eosinophil reduction". AstraZeneca contended that "there are currently no data directly comparing the implications of MOA [mechanism of action] differences between the three treatments". AstraZeneca continued to say that "in the absence of further data, we therefore believe it is appropriate to assume equivalent efficacy between benralizumab and reslizumab in the model". The ERG, however, considered this still to be a very strong assumption and not evidence based, although there was no clear option for an appropriate analysis.

4.3.5 Studies included in MAIC for the comparison between benralizumab and mepolizumab

4.3.5.1 Studies for benralizumab

Following the application of the inclusion criteria for MAIC (Table 26, reproduced from CS Section B.2.9, Table 28, pp. 117-118) to the results of the SLR, seven benralizumab studies were considered for inclusion in the MAIC analysis.

4.3.5.1.1 Excluded studies

Four studies were excluded: three for being Phase II studies and one for early termination. These exclusions were discussed in Section 4.1.3.1 above.

4.3.5.1.2 Included studies

Three benralizumab trials were included in AstraZeneca's MAIC analysis. These were SIROCCO [11], CALIMA [12] and ZONDA [13].

Table 31 Summary of key design characteristics for each trial

Study	Sample size	Treatment	Age and gender*	Baseline medication	History of exacerbations
SIROCCO (Bleecker 2016)	1205	Benralizumab 30mg Q4W Benralizumab 30mg Q8W Placebo	Age 12-75 eligible, mean (SD) = 48.8 (14.3); Gender 34% male	High-dose (>500 µg) ICS plus LABA with/without additional asthma controller(s)	2 or more exacerbations in past year
CALIMA (FitzGerald 2016)	1306	Benralizumab 30mg Q4W Benralizumab 30mg Q8W Placebo	Age 12-75 eligible, mean (SD) = 49.3 (14.4); Gender 38% male	Medium-to-high (high defined as >500 µg) dose ICS plus LABA with/without additional asthma controller(s)	2 or more exacerbations in past year
ZONDA (Nair 2017)	220	Benralizumab 30mg Q4W Benralizumab 30mg Q8W Placebo	Age 18-75 eligible, mean (SD) = 51.0 (11.3);	High-dose (>500 µg) ICS and chronic OCS without or without	1 or more exacerbations in past year

			Gender 39% male	additional asthma controller	

* = Overall values re-calculated from group-specific values in CS, Section B.2.3, Tables 13-15, pp.78-84

4.3.5.2 Studies for mepolizumab

Six mepolizumab studies were considered for inclusion in the MAIC analysis according to the inclusion criteria (Table 26, reproduced from CS Section B.2.9, Table 28, pp. 117-118).

4.3.5.2.1 Excluded studies

Two studies were excluded as a consequence of being Phase II studies, which was in accordance with the company's stated inclusion criteria for MAIC analysis. These were the Haldar 2009 [37] and Nair 2009 [38] studies. One further mepolizumab study, MUSCA [39], was excluded from the base case MAIC, but is included as a scenario analysis. The stated rationale for this decision was that MUSCA was "designed to assess HRQoL as a primary outcome and not powered to detect differences in efficacy outcomes" (CS Section D.1.2, Table 14, p.348). AstraZeneca's stated inclusion criteria for the MAIC analysis did not specify that the eligible outcome for the MAIC analysis had to be the primary outcome of the study on which the study was powered. The CS also stated that the follow-up period for MUSCA was shorter than for the other trials, but this was not listed as an exclusion criterion. Therefore, the exclusion of the MUSCA trial from the base case MAIC appeared methodologically inappropriate. Moreover, as discussed in Section 4.4.7, in both MUSCA scenario MAIC analyses, after matching,

[redacted]

There was one additional mepolizumab study [40], mentioned in stakeholder comments on the NICE mepolizumab appraisal, which the ERG noted AstraZeneca had not taken into consideration in its submission. It was a secondary analysis of data from the DREAM and MENSA studies, and as such did not include any additional trials beyond what the company had included in its MAIC analysis. This secondary analysis assessed the effect of differing eosinophil thresholds on asthma exacerbation rate reduction. The ERG did not consider that this analysis should have been included in the MAIC, but considered that its exclusion should have been listed and justified.

4.3.5.2.2 Included studies

Three mepolizumab studies were included in AstraZeneca's base case MAIC analysis. These were MENSA [41], DREAM [42] and SIRIUS [43].

Table 32 Summary of key design characteristics for each trial

Information about comparator trials was taken from the CS where available, and also from relevant trial publications

Study	Sample size	Treatment	Age and gender*	Baseline medication	History of exacerbations
MENSA (Ortega 2014)	580	Mepolizumab, 100 mg Q8W SC Mepolizumab, 75mg Q4W IV Placebo	Age mean (range) = 50.0 (12-82); Gender 43% male	High dose (≥800 µg) ICS plus additional controller	At least two exacerbations in past year
DREAM (Pavord 2012)	621	Mepolizumab, 75 mg Q4W IV Mepolizumab 250 mg Q4W IV Mepolizumab 750 mg Q4W IV Placebo	Age 12-74 eligible, mean (SD) = 48.7 (11.2); Gender 27% male	High dose (≥800 µg) ICS plus additional controller	At least two exacerbations in past year
SIRIUS (Bel 2014)	135	Mepolizumab 100 mg Q4W SC Placebo	Age 12 and over eligible, mean (range) = 50 (16-	High dose (≥800 µg) ICS plus additional controller	Not stated

			74); Gender 45% male		

* Overall values were re-calculated where necessary from group-specific values in trial publications

4.3.6 Risk of bias in studies included in MAIC for the comparison between benralizumab and mepolizumab

4.3.6.1 Studies for benralizumab

Risk of bias assessment for the three benralizumab trials included in MAIC analysis was presented above in Section 4.1.4 above. The key issue identified for the benralizumab trials that may affect the validity of the MAIC analysis, and its use to select clinical inputs to the model, was that selective outcome reporting was present in the CS for all three trials whereby many outcomes listed in the protocol were not reported. Moreover, the unreported outcomes nocturnal awakening and change in rescue medication use [redacted]

4.3.6.2 Studies for mepolizumab

Table 33 Risk of bias assessment for MENSA trial

Quality assessment of RCTs was undertaken using the minimum criteria for assessment of risk of bias in RCTs as described in guidance by the Centre for Reviews Dissemination (CRD) [27].

Item	PenTAG Judgement
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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 ERG's assessment of risk of bias in the MENSA trial for mepolizumab identified one area of concern, namely that no detail was reported regarding the allocation concealment method.

Table 34 Risk of bias assessment for DREAM trial

Item	PenTAG Judgement
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes

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 ERG's assessment of risk of bias in the DREAM trial for mepolizumab identified one area of concern. While all the key clinical efficacy outcomes were included in the trial report, some additional outcomes such as number of all recorded exacerbations per year and mean change from baseline in post-bronchodilator FEV1 were not. However, it is important to note that all the key outcomes were reported.

Table 35 Risk of bias assessment for SIRIUS trial

Item	PenTAG Judgement
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

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 ERG's assessment of risk of bias in the SIRIUS trial for mepolizumab identified one area of concern, namely that no detail was reported regarding the allocation concealment method. Additionally, the proportion of women differed between the arms, but since the arms were otherwise well balanced and this was a demographic rather than key clinical difference, the ERG considered that the study groups were similar at the study outset.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Summary of analyses undertaken

Anchored MAIC analysis was performed to compare the treatment effects of benralizumab and mepolizumab. The base case MAIC analysis for exacerbation trials used data from SIROCCO/CALIMA versus MENSA/DREAM (CS Section B.2.9, p.120), while that for OCS-sparing trials used data from ZONDA versus SIRIUS (CS Section B.2.9, p.122). This reflected the outcomes of each trial, and appeared appropriate. The overall approach to preparing and conducting the MAIC was in accordance with NICE DSU recommendations. The ERG considered MAIC to be an appropriate analytical framework to use since AstraZeneca only had access to IPD for the benralizumab trials and summary data for the mepolizumab trials. However, NICE DSU guidelines recommend either MAIC or simulated treatment comparisons (STC) for this situation. The CS makes brief mention of why MAIC was preferred to STC, "on the basis that it avoids the need to assume a relationship between the effect outcome, e.g., exacerbation rates, and the 'matching' characteristic" (CS section B.2.9., p.114). The ERG considered this to be a reasonable argument, although did not have access to IPD in order to verify this. Additionally, the CS could have offered a more detailed justification for the preference for MAIC over STC.

4.4.2 Use of anchored MAIC comparison

AstraZeneca conducted anchored MAIC analysis for the comparison between benralizumab and mepolizumab (CS B.2.9, p.114). Anchored MAIC analysis was made possible by the presence of a common control group in the form of placebo. NICE DSU guidelines recommended the use of anchored MAIC rather than unanchored MAIC wherever the

anchored approach is feasible. In particular, unanchored MAIC analysis requires that "absolute outcomes can be reliably predicted into the aggregate AC trial. In practice, reliable prediction of this kind is very hard to obtain – it can only be achieved if the joint covariate set includes *every* prognostic variable and effect modifier acting in the AC trial". In contrast, anchoring offers some protection in the case where certain relevant prognostic factors or effect modifiers are not available. Indeed, NICE DSU guidelines cautioned that "It is impossible to guarantee that all prognostic variables and effect modifiers are known or available." Therefore, the ERG considered the anchored model presented by AstraZeneca to be the appropriate choice.

4.4.3 Comparison of study and baseline characteristics of included trials

AstraZeneca reported a thorough comparison of the study and baseline characteristics of the trials included in the MAIC analysis (CS Section D.1.2, pp.352-360). The ERG reproduced key information from the CS below:

Table 36 Summary of study characteristics of benralizumab and mepolizumab studies

Study characteristics	Benralizumab		Mepolizumab	
	SIROCCO	**CALIMA**	**MENSA**	**DREAM**
Publication type	Journal and CSR	Journal and CSR	Journal and CSR	Journal and CSR
	Benralizumab 30 Q4W SC	Benralizumab 30 Q4W SC	Mepolizumab 75 mg Q4W IV	Mepolizumab 75 Q4W mg IV
Interventions	Benralizumab 30 mg Q8W SC	Benralizumab 30 mg Q8W SC	Mepolizumab 100 mg Q4W SC	Mepolizumab 250 mg Q4W mg IV
	Placebo	Placebo	Placebo	Mepolizumab 750 mg Q4W mg IV
	-	-	-	Placebo
Phase	III	III	III	III
Sample size	1205 (805)*	1306 (734)*	580	308
Method of randomisation	Adequate	Adequate	Adequate	Adequate
Blinding status	Double-blind	Double-blind	Double-blind	Double-blind
Study duration	48 weeks	64 weeks	46 weeks	58 weeks
Treatment duration	48 weeks	56 weeks	32 weeks	52 weeks

Primary outcome	Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs. placebo with baseline blood EOS ≥300 cells/μL	Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs. placebo with baseline blood EOS ≥300 cells/μL	Rate of clinically significant exacerbations	Rate of clinically significant exacerbations
Secondary outcomes	• Pre-bronchodilator FEV1 and post-bronchodilator FEV1 • Asthma symptom score (total, daytime, and night-time) • Rescue medication use • Morning and evening PEF • Nights with awakening due to asthma • ACQ-6 • Time to first asthma exacerbation • Proportion of patients with ≥1 asthma exacerbation • AQLQ[S]+12 • EQ-5D 5L	• Pre-bronchodilator FEV1 and post-bronchodilator FEV1 • Asthma symptom score (total, daytime, and night-time) • Rescue medication use • Morning and evening PEF • Nights with awakening due to asthma • ACQ-6 • Time to first asthma exacerbation • Proportion of patients with ≥1 asthma exacerbation • AQLQ[S]+12 • EQ-5D 5L • Annual rate of asthma exacerbations associated with an ER/urgent care visit or a hospitalisation • WPAI + CIQ	• Frequency of exacerbations requiring hospitalisation or ED visit • Frequency of exacerbations requiring hospitalisation • Pre-bronchodilator FEV1 • SGRQ • ACQ-5 • Percentage of patients recording a favourable treatment response as measured by the Subject Rated Response to Therapy • Percentage of patients evaluated as having a favourable treatment response as measured by the Clinician Rated Response to Therapy • Daily salbutamol/albuterol use • Daily asthma symptom scores • Awakening at night due to asthma symptoms requiring rescue medication use • Morning PEF • Post-bronchodilator FEV1 • Number of days with OCS taken for exacerbations	• Time to first exacerbation requiring hospitalisation or ED visit • Frequency of exacerbations requiring hospitalisation or ED visit • Time to first exacerbation requiring hospitalisation or ED visit • Frequency of investigator-defined exacerbations • Time to first investigator-defined exacerbation • Pre-bronchodilator FEV1 • Post-bronchodilator FEV1 • ACQ-6 score • Proportion of patients with a reduction in exacerbations from baseline of ≥40% • Daily salbutamol/albuterol use • Daily asthma symptom scores

	• Annual rate of asthma exacerbations associated with an ER/urgent care visit or a hospitalisation • WPAI + CIQ • Asthma-specific resource utilisation (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • CGIC • PGIC • Safety	• Asthma-specific resource utilisation (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • CGIC • PGIC • Safety	• Prednisone (or equivalent) exposure per exacerbation • Time to withdrawal due to asthma exacerbations • Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits • Time to first exacerbation requiring hospitalisation or ED visit • IgE count • VAS score (in patients with nasal polyps) • Safety	• Awakening at night due to asthma symptoms requiring rescue medication use • Morning PEF • Clinician rating score of response to therapy • Subject rating score of response to therapy • Number of days with OCS • Time to withdrawal due to asthma exacerbations • Time to premature discontinuation • Safety •

The highlighted cells indicate differences across the trials. *Number in parenthesis represents a number of patients for BENRA Q8W and placebo arms

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life; BENRA: Benralizumab; CGIC: Clinician global impression of change; CIQ: Classroom Impairment Questions; CSR: Clinical Study Report; ED: Emergency Department; EOS: Eosinophil; EQ-5D: European Quality of life-5D; ER: Emergency room; FEV1: Forced expiratory volume in one second; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IV: Intravenous; LABA: Long-acting beta-2 agonist; OCS: Oral corticosteroid; PEF: Peak expiratory flow; PGIC: Patient Global Impression of Change; Q4W: every four weeks; Q8W: every eight weeks; SC: subcutaneous; SGRQ: St. George Respiratory Questionnaire; WPAI: Work Productivity and Activity Impairment; VAS

Source: company submission section D.1.2 table 150, pp.354-355.

Table 37 Overview of inclusion/exclusion criteria of benralizumab and mepolizumab studies included in the analysis

Characteristics	Benralizumab		Mepolizumab	
	SIROCCO	CALIMA	MENSA	DREAM
Age	12-75 years		12-82 years	12-74 years
Weight	≥40 kg	≥45 kg		

Baseline medication for asthma	High-dose ICS (adults: >500 µg of FP or equivalent) + LABA ± OCS or any other controller	Medium (>250-500 µg of FP or equivalent) to high-dose ICS (adults: >500 µg of FP or equivalent) + LABA ± OCS or any other controller	High-dose ICS (for ages ≥18 years: ≥880 µg of FP or equivalent; for ages <18 years: ≥440 µg FP or equivalent) + LABA or any other controller ± OCS	High-dose ICS (≥880 µg of FP or equivalent) + LABA or any other controller ± OCS
High-dose ICS definition	For 18 years and above: • >500 µg/day FP or equivalent daily • For ICS/LABA combination preparations, the highest approved maintenance dose in the local country would have met this ICS criterion For ages 12-17 years: • >500 µg/day FP or equivalent daily • For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country would have met this ICS criterion	• >500 µg FP equivalents total daily dose (and LABA) for at least 6 months prior to Visit 1 • For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country would have met this ICS criterion	For 18 years and above: • ICS dose must be ≥880 µg/day FP (ex-actuator) or equivalent daily • For ICS/LABA combination preparations, the highest approved maintenance dose in the local country For ages 12-17 years: • ICS dose must be ≥440 µg/day FP (ex-actuator) or equivalent daily • For ICS/LABA combination preparations, the highest approved maintenance dose in the local country	
Exacerbation history	≥2 exacerbations in the past year requiring systemic corticosteroid use or temporary increase in the patient's usual maintenance OCS dosage		≥2 exacerbations in the past year requiring systemic corticosteroid use or a ≥2-fold increase in maintenance OCS dose	

Eosinophilic asthma	No restriction for specific EOS cut-offs	Blood EOS ≥150/μL at screening OR ≥300/μL in past year	Eosinophilic asthma according to either of following: ≥300/μL blood EOS count in previous year, or ≥3% sputum EOS, or an exhaled NO concentration of 50 ppb or more, or prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or OCS
Pre-bronchodilator FEV1 % predicted	<80% (<90% for patients 12-17 years of age)	<80% (<90% for patients 12-17 years of age)	<80%

The highlighted cells indicate differences across the trials.
EOS: Eosinophil; FEV1: Forced expiratory volume in one second; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2 agonist; NO: Nitric oxide; OCS: Oral corticosteroid; SC: subcutaneous
Source: company submission section D.1.2 table 151, pp.356-357

Table 38 Comparison of baseline characteristics of patients included in benralizumab and mepolizumab studies

Characteristics	SIROCCO		CALIMA		MENSA			DREAM	
Population	Overall		HD ICS subgroup		Overall			Overall	
	BENRAQ8W N=398	Placebo N=407	BENRAQ8W N=364	Placebo N=370	MEPO 100 mg SC N=194	MEPO 75 mg IV N=191	Placebo N=191	MEPO 75 mg IV N=153	Placebo N=155
Age, years	47.6 (14.5)	48.7 (14.9)	50.1 (13.3)	49.8 (14.3)	51.2 (14.55)	50.0 (14.03)	49.2 (14.26)	50.2 (11.3)	46.4 (10.8)
Gender, % male	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0	37.0
White, % patients	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0	90.0
Black, % patients	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0	4.0
Asian, % patients	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0	6.0
Other, % patients	11.6	9.6	0.3	0.0	1.0	1.0	1.0	1.0	0.0
Body mass index	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.60 (5.58)	27.68 (5.68)	28.04 (5.58)	28.4 (6.0)	28.3 (6.1)
FEV1 predicted (%)	56.1[$]	56.6[$]	56.9	57.5	59.3	61.4	62.4	60[$]	59[$]
Morning PEF (L/min)	233.12	230.83	241.85	242.16	255.3	268.6	277	-	-
FEV1/FVC (%)	65	66	64	65	66	67	67	68	67
FEV1 pre-bronch. (L)	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81$	1.90$
Reversibility (%)	27.2	25.5	25.1	27.2	27.9[$]	25.4[$]	27.4[$]	22.6^	26.8^
ACQ scores**	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2	2.5
Exacerbations in previous year	2.8	3	2.7	2.8	3.8	3.5	3.6	>3~	>3~
2 exacerbations in previous year (% patients)	63.3	60	62.9	63.5	38	43	47	46	42

≥3 exacerbations in previous year (% patients)	36.68	40	36.81	36.49	61.86	57.07	52.88	54	57
Never smokers (% patients)	82.2	80.6	78.02$	78.92$#	74$#	73$	70$	80$	78$
OCS use (% patients)	17.8	16.2	10.71$	11.08$#	27$#	25$	23$	30.07$	29.03$
EOS ≥300 cells/µL (% patients)	67.08	65.6	65.6	67.02	43.2	41.3	41.8	56.2	45.16
EOS <300 cells/µL (% patients)	32.9	34.3	34.3	32.9	54.6	55.4	56.5	43.7	54.8
EOS (cells/µl)	369.8	456.5	463.4	490.8	290*	280*	320*	250*	280*
IgE levels	-	-	-	-	149.72*	180.32*	150.12*	-	-
Atopic status	61.3	56.5	61.5	63.0	-	-	-	51.0	52.0
Nasal polyps	23.2	23.2	16.8	18.1	14.4	16.7	17.2	7.0	10.0

The highlighted cells indicate differences across benralizumab and mepolizumab trials.

"Overall" for SIROCCO, MENSA and DREAM refer to a population receiving high-dose ICS. The data in the table represent mean (SD) values unless otherwise indicated. **ACQ-6 in SIROCCO, CALIMA, and DREAM; ACQ-5 in MENSA. $The data are extracted from the respective publications. All other values are extracted from the respective CSR; #Calculated from the reported subgroup data. ~Calculated from the reported frequency of exacerbations; ^Data reported at screening visit; *Geometric means

ACQ: Asthma Control Questionnaire; BENRA: Benralizumab; CSR; Clinical study report; EOS: Eosinophil; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; HD: High-dose; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; PEF: Peak expiratory flow; Q8W: every eight weeks; SD: Standard deviation

Source: company submission section D.1.2 table 152, pp.358-359

Table 39 Definition of clinically significant exacerbations reported across the studies included for analysis

Outcome	Study name	Outcome definition
Clinically significant exacerbations	SIROCCO	An exacerbation was defined as a worsening of asthma that led to any of the following: (i) use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depot-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids; (ii) an ER/urgent care visit (defined as evaluation and treatment for <24 hours in an ED or urgent care centre) due to asthma that required systemic corticosteroids (as per above); (iii) an inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma
	CALIMA	
	MENSA	An exacerbation was defined as worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days or the patient visited an ED or was hospitalised
	DREAM	Clinically significant exacerbations were defined as worsening of asthma requiring use of oral corticosteroids for 3 or more days, admission, or a visit to the ED

ED: Emergency department; ER: Emergency room; OCS: Oral corticosteroid
Source: company submission section D.1.2 table 153, p.360

The CS admitted that there were "key differences in the baseline characteristics of the benralizumab and mepolizumab studies" (CS Section D.1.2, p.353). The following text (quoted from CS Section D.1.2, p.353) provides a summary of these differences:

- "Baseline EOS count: The inclusion criteria in MENSA required that patients should have an EOS count of ≥150 cells/μL at baseline or ≥300 cells/μL in the previous year, while the DREAM trial required patients to meet multiple criteria (either blood EOS ≥300 cells/μL in prior year, sputum EOS ≥3%, exhaled nitric oxide ≥50 ppb, or prompt deterioration after corticosteroid dose reduction). However, these inclusion parameters were not a requirement in the benralizumab studies
- Definition of high-dose ICS: In the benralizumab studies, the definition for the high-dose ICS was >500 μg of FP daily or equivalent, while in the mepolizumab studies it was ≥880 μg of FP daily or equivalent if ICS was used alone. For the ICS/LABA combinations, the highest approved maintenance dose of ICS was as per the study country recommendations across both the trials
- Prior history of exacerbations: The mepolizumab studies recruited ~60% patients with a history of three or more exacerbations, while the benralizumab studies recruited ~40% patients with a history of three or more exacerbations in the previous year

- Baseline OCS use: The mepolizumab studies recruited a population with more severe asthma, as indicated by ~23%-30% of patients using OCS at baseline, while in the benralizumab studies, the percentage of patients using OCS at baseline ranged from 11% to 18%
- Treatment duration: The studies varied in terms of duration of follow-up, ranging from 32 weeks to 56 weeks (SIROCCO: 48 weeks, CALIMA: 56 weeks; MENSA: 32 weeks, and DREAM: 52 weeks)"

The ERG agreed with AstraZeneca that there were notable differences between the benralizumab trials and the mepolizumab trials as outlined in the tables and bullet points presented above. AstraZeneca, elsewhere in their submission (CS Section B.3.3, p.162-163), cited 'key differences' between the baseline trial populations as reason not to conduct a MAIC analysis comparing benralizumab and reslizumab. However, the issue for the reslizumab comparison was that the differences between the trial populations were such that the available effective sample size would have been reduced to 20. In contrast, the available effective sample size for the MAIC analysis of exacerbation trials (SIROCCO/CALIMA versus MENSA/DREAM) was 639 (CS Section D.1.2, Table 155, p.366). Therefore, on balance, the ERG agreed with AstraZeneca that the baseline differences between the benralizumab trials and the mepolizumab trials did not preclude MAIC analysis or render it intrinsically inappropriate. The ERG asked AstraZeneca for further clarification on this matter (ERG's clarification question, A9) and the response received (Company response to clarification question, A9) was satisfactory in terms of its reference to issues of effective sample size in relevant NICE TSD guidelines. In particular, the potential comparison with reslizumab had a very low effective sample size (ESS) and a highly skewed distribution of weights, indicating issues with population overlap. AstraZeneca's response stated that for the comparison between benralizumab and mepolizumab, "a sufficient overlap was present as judged by the distribution of characteristics across the studies, weight distribution and ESS. The ESS was large enough to obtain reliable effect estimates with sufficient precision (ESS>400 for all scenarios)".

4.4.4 Effect modifier selection

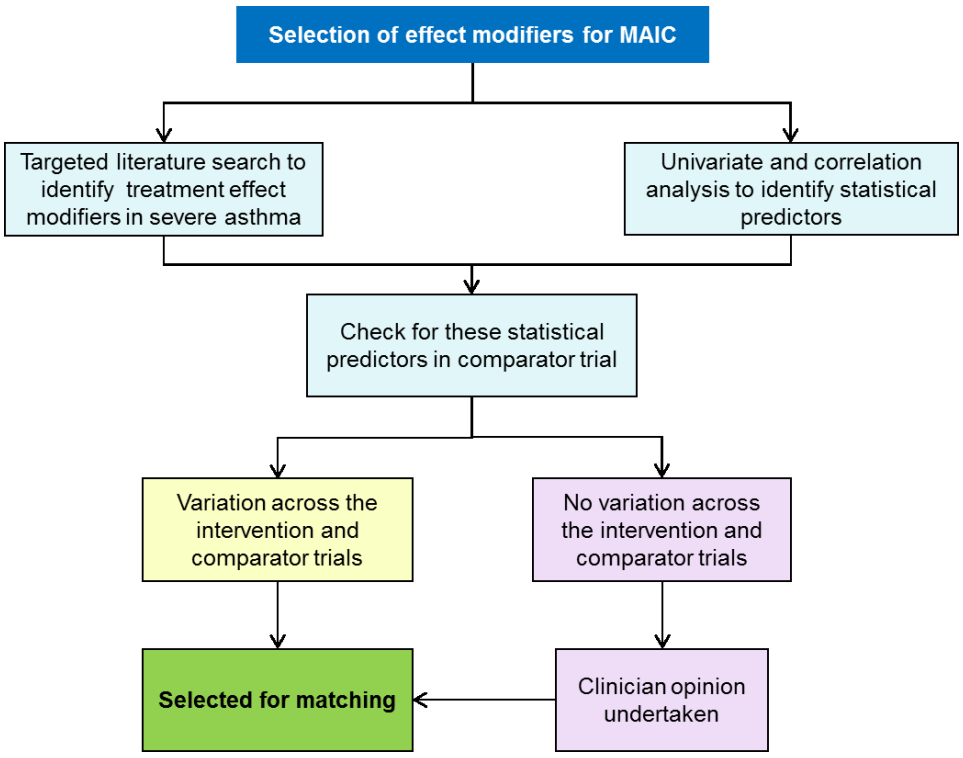
An important step in a MAIC analysis, according to NICE DSU recommendations, is the selection of effect modifiers and prognostic factors. This material was covered in detail in the Appendix of the CS (Section D.1.2, pp.361-365, pp.383-387). The NICE DSU recommendations stated that all known effect modifiers should be included in the MAIC analysis regardless of whether or not they are imbalanced between the included trials (NICE DSU 18, Figure 4, p.76). NICE DSU also recommend not to include variables that are purely prognostic factors in anchored MAIC analysis.

AstraZeneca used an approach based on a combination of literature searches and clinical opinion to identify effect modifiers and prognostic factors, although the CS referred exclusively here to 'effect modifiers'. For example, for the exacerbation trials, the CS reported that a sequential approach was taken as follows (CS Section D.1.2, pp.361-362):

1. "Univariate regression and correlation analyses were run to check the significance of variables on each of the outcomes, followed by a multivariate analysis to find the set of variables that explain the maximum variations present in the outcome of interest
2. These variables were then checked for reporting in the comparator trial and assessed for differences across the trials
3. Additionally, a targeted literature search was carried out to ascertain whether these variables have been associated with treatment effect modification in severe asthma. As per the review published by Schleich et al., blood EOS count, exacerbation history in the previous 12 months, and IgE status have been considered to be established biomarkers in severe asthma [44].
4. Moreover, the use of OCS is known to be an indicator of disease severity, so it was also considered as an effect modifier in the analysis [45]. In addition, the gender of the patient was found to be significantly associated with all the primary endpoints. Although it is a prognostic variable, it was also considered for matching due to its significant impact and the weight it contributed after matching. No significant impact on the results was observed when we chose to drop or keep this variable for matching.
5. Furthermore, two additional variables including nasal polyps and BMI were selected for matching after consultation with three external clinical experts"

The ERG did have some concerns about the identification of effect modifiers and the clarity of reporting in that section of the CS. The view of the ERG was that the steps outlined in the selection of effect modifiers may not be sufficient to identify all established effect modifiers. The CS stated that "The variables selected for adjustment in the MAIC were selected in an ordered way and were validated with external key opinion leaders" (CS Section B.2.9., P.115). It was unclear whether clinical input was only sought on the validity of a selection of variables that had already been made, rather than seeking open elicitation of potential effect modifiers from clinicians from the onset. The pathway diagram presented in the CS did suggest that AstraZeneca potentially only sought clinical opinion on effect modifiers selected based on the basis of a literature search and statistical analysis, and did not allow clinicians to suggest potential effect modifiers afresh. The NICE Guide to the Methods of Technology Appraisal (Section 5.2.7) explicitly states that effect modifiers must be 'pre-specified and clinically plausible', and that effect modifiers should either be identified from a review of the literature or from clinical input. The guidance does not suggest that clinical input should be restricted to commenting on already identified modifiers. If clinical input has only been sought on already identified factors, this would contribute clinically relevant effect modifiers being missed.

Figure 12 Sequential approach adopted to select effect modifiers for matching in the MAIC



Source: company submission section D.1.2, figure 44, p.363

The CS stated that variables from the univariate regression were "checked for reporting in the comparator trial and assessed for differences across the trials" (CS Section D.1.2,

p.361). However, the above figure suggested that this process was also undertaken for effect modifiers identified from the literature search

A table is provided in the CS outlining which variables were selected for matching in the MAIC.

Table 40 Summary of selection of variables for matching in the MAIC

Variable	Definition	Statistical significance* (p<0.05)	Information available in MEPO trials	Difference between BENRA and MEPO trials	Effect modifier	Selected for matching
Age	Mean (SD)	No	Yes	No	-	No
Gender	Categories: male, female	Yes	Yes	Yes	-	Yes
Race	Categories: White, Asian, Black or African American	Yes	Yes	No	-	No
BMI	Mean (SD)	Yes	Yes	No	-	Yes (based on clinician opinion)
FEV1 predicted (%)	Mean (SD)	Yes	Yes	No	-	No
FEV1/FVC (%)	Mean (SD)	No	Yes	No	-	No
FEV1 reversibility (%)	Mean (SD)	No	Yes	No	-	No
ACQ score	Mean (SD)	Yes	Yes	Yes	-	No (different ACQ scale versions used)
No. of exacerbations in previous 12 months	Categories :2 exacerbations, >2 exacerbations	Yes	Yes	Yes	Yes	Yes
Nicotine status	Categories: former, never	Yes	Yes	No	-	No
OCS use at baseline	Categories: yes, no	Yes	Yes	Yes	Yes	Yes
EOS count	Categories: EOS<300/µL, EOS≥300/µL	Yes	Yes	Yes	Yes	Yes
IgE status	Categories: IgE ≤30 IU/mL, IgE >30-≤700 IU/mL, IgE >700 IU/mL	Yes	Yes	Yes	Yes	Yes
Atopic status	Categories: yes, no	No	No	-	-	No

Nasal polyps	Categories: yes, no	Yes	Yes	No	-	Yes (based on clinician opinion)

Source: company submission section D.1.2 table 154, p.364

In the identification process for potential effect modifiers, the ERG believe that interaction analysis should have also been conducted as well as univariate regression and correlation analysis. Moreover, the ERG noted from the above table that certain variables that were statistically significant – age, race, BMI, FEV_1, nicotine status, and atopic status – were excluded as effect modifiers and not selected for matching in MAIC because there was not a significant imbalance between benralizumab and mepolizumab trials. These exclusions contradicted NICE DSU recommendations (NICE DSU 18, Figure 4, p.76) that all known effect modifiers should be included in the MAIC analysis regardless of whether or not they are imbalanced between the included trials. The CS reported the NICE DSU recommendations (CS Section D.1.2, p.361) to say that "the effect modifiers selected should be in sufficient imbalance between included studies". Instead, the NICE DSU recommendations state that finding unbalanced effect modifiers helps justify the anchored MAIC analysis, but that all effect modifiers should be included regardless of whether they are imbalanced between trials. The variable ACQ score was dropped (shown in table above) even though it was both statistically significant and shown to be in imbalance between the benralizumab and mepolizumab trials. The reason provided for this exclusion was that trials used different versions of the ACQ score (CS Section D.1.2).

4.4.5 Comparison of baseline characteristics of included trials after matching

AstraZeneca additionally presented a comparison of baseline characteristics of included trials after matching. The tables below reproduced from the CS presented the results of AstraZeneca's analysis for the exacerbation trials:

Table 41 Comparison of baseline characteristics of patients before and after matching for the analysis of annual rate of clinically significant exacerbations and annual rate of exacerbations leading to ED visit or hospitalisation

Baseline characteristics		SIROCCO/CALIMA (before adjustment)	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment for MENSA/DREAM)
		BENRA Q8W + placebo ICS (≥880 µg FP daily) N=959	MEPO 75 mg IV + MEPO 100 mg SC + placebo (≥880 µg FP daily) N=884	ESS=639
Eosinophil count	≥300/µL	67.05	52.45	52.75
	<300/µL	32.95	47.55	47.25
Maintenance OCS use	Yes	15.22	26.58[$]	30.18
	No use	84.78	73.42[$]	69.82
IgE count	<30 IU/mL	11.55	13.29	14.66
	>30-≤700 IU/mL	71.19	70.35	70.02
	>700 IU/mL	17.27	16.35	15.32
Gender	Male	36.60	40.16	39.2
	Female	63.40	59.95	60.8
Exacerbations in the previous 12 months	2	61.63	42.99	42.69
	>2	38.38	56.79	57.31
Nasal polyps	Yes	81.33	86.83	83.44
	No	18.67	13.17	16.56
Baseline BMI	Mean (SD)	29.89 (6.27)	27.98 (5.912)	28.37 (6.13)

Data are available for 944 patients; $The data are extracted from the respective publications. All other values are extracted from the respective CSRs. Data for the SIROCCO/CALIMA trials are calculated from IPD

BENRA: Benralizumab; BMI: Body mass index; CSR: Clinical study report; ED: Emergency department; ESS: Effective Sample Size; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IPD: Individual patient data; IU: International units; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q8W: Every 8 weeks; SC: Subcutaneous; SD: Standard deviation

Source: company submission section D.1.2 table 155, pp.366-367.

Table 42 Comparison of baseline characteristics of patients before and after matching for the analysis of change from baseline in pre-bronchodilator FEV1 at 32 weeks

Baseline characteristics		SIROCCO/CALIMA (before adjustment)	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment for MENSA/DREAM)
		BENRA Q8W + placebo ICS (≥880 µg FP daily) N=863	MEPO 75 mg IV + MEPO 100 mg SC + placebo (≥880 µg FP daily) N=884	ESS=559
Eosinophil count	≥300/µL	68.02	52.45	52.43
	<300/µL	31.98	47.55	47.57
Maintenance OCS use	Yes	15.06	26.58$	30.24
	No use	84.94	73.42$	69.76
IgE count	<30 IU/mL	11.40	13.29	14.62
	>30-≤700 IU/mL	71.09	70.35	70.01
	>700 IU/mL	17.51	16.35	15.37
Gender	Male	37.43	40.16	39.08
	Female	62.57	59.95	60.92
Exacerbations in previous year	2	62.34	42.99	42.82
	>2	37.66	56.79	57.18
Nasal polyps	No use	81.23	86.83	83.09
	Yes	18.77	13.17	16.91
Baseline BMI	Mean (SD)	28.89 (6.27)	27.98 (5.912)	28.38 (6.15)

Data are available for 851 patients; $The data are extracted from the respective publications. All other values are extracted from the respective CSRs. Data for the SIROCCO/CALIMA trials are calculated from IPD
BENRA: Benralizumab; BMI: Body mass index; CSR: Clinical study report; ESS: Effective sample size; FEV1: Forced expiratory volume in one second; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IPD: Individual patient data; IU; International unit; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q8W: Every 8 weeks; SC: Subcutaneous; SD: Standard deviation
Source: company submission section D.1.2 table 156, p.368

Table 43 Comparison of baseline characteristics of patients before and after matching for the analysis of change from baseline in pre-bronchodilator FEV1 (L) at the end of studies

Baseline characteristics		SIROCCO/CALIMA (before adjustment)	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment for MENSA/DREAM)
		BENRA Q8W + placebo ICS (≥880 µg FP daily) N=838	MEPO 75 mg IV + MEPO 100 mg SC + placebo (≥880 µg FP daily) N=884	ESS=540
Eosinophil count	**≥300/µL**	67.66	52.45	52.72

	<300/µL	32.34	47.55	47.28
Maintenance OCS use	**Yes**	14.68	26.58$	29.83
	No use	85.32	73.42$	70.17
IgE count	**<30 IU/mL**	11.00	13.29	14.15
	>30-≤700 IU/mL	71.34	70.35	70.39
	>700 IU/mL	17.65	16.35	15.45
Gender	**Male**	36.99	40.16	39.25
	Female	63.01	59.95	60.75
Exacerbations in previous year	**2**	62.65	42.99	43.2
	>2	37.35	56.79	56.8
Nasal polyps	**No use**	80.79	86.83	82.99
	Yes	19.21	13.17	17.01
Baseline BMI	**Mean (SD)**	28.84 (6.32)	27.98 (5.912)	28.36 (6.10)

Data are available for 827 patients; $The data are extracted from the respective publications. All other values are extracted from the respective CSRs. Data for the SIROCCO/CALIMA trials are calculated from IPD
BENRA: Benralizumab; BMI: Body mass index; CSR: Clinical study report; ESS: Effective sample size; FEV1: Forced expiratory volume in one second; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IPD: Individual patient data; IU: International units; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q8W: Every 8 weeks; SC: Subcutaneous; SD: Standard deviation
Source: company submission section D.1.2 table 157, pp.369-370

Table 44 Comparison of baseline characteristics of patients before and after matching for the analysis of change from baseline in pre-bronchodilator FEV1 (L) at the end of studies (after excluding MENSA trial)

Baseline characteristics		**SIROCCO/CALIMA (before adjustment)**	**DREAM (aggregate reported data)**	**SIROCCO/CALIMA (after adjustment for DREAM)**
		BENRA Q8W + placebo ICS (≥880 µg FP daily) N=838	**MEPO 75 mg IV + placebo (≥880 µg FP daily) N=884**	**ESS=402**
Eosinophil count	**≥300/µl**	67.66	41.88	42.78
	<300/µL	32.34	58.12	57.22
Maintenance OCS use	**Yes**	14.68	30.84$	36.22
	No use	85.32	69.16$	63.78
IgE count	**<30 IU/mL**	11.00	12.34	14.95
	>30-≤700 IU/mL	71.34	70.45	70.81
	>700 IU/mL	17.65	16.88	14.25
Gender	**Male**	36.99	34.74	33.72
	Female	63.01	65.26	66.28
Exacerbations in previous year	**2**	62.65	43.83	41.75
	>2	37.35	55.84	58.25

Nasal polyps	**No use**	80.79	91.3	89.63
	Yes	19.21	8.7	10.37
Baseline BMI	**Mean (SD)**	28.84 (6.32)	28.35 (6.05)	29.12 (6.48)

Data available for 827 patients; $The data are extracted from the respective publications. All other values are extracted from the respective CSRs. Data for the SIROCCO/CALIMA trials are calculated from IPD
BENRA: Benralizumab; BMI: Body mass index; CSR: Clinical study report; ESS: Effective sample size; FEV1: Forced expiratory volume in one second; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IPD: Individual patient data; IU: International units; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q8W: Every 8 weeks; SC: Subcutaneous; SD: Standard deviation
Source: company submission section D.1.2 table 158, p.371

The ERG are satisfied that the data presented above demonstrated that the MAIC analysis for the exacerbation trials had adequately re-weighted the data from the trials for which IPD were available to match the competitor trials for which only aggregate data were available. Matching cannot always produce identical characteristics between trial populations, and small differences remained. The ERG did, however, note that the CS did not report this detailed assessment for the OCS-sparing trials.

4.4.6 Correspondence to NICE target population

As discussed above, the MAIC analyses in the CS contained a population that included adolescents from age 12 upwards, whereas the NICE scope population was adults, taken to mean from age 18 upwards. As discussed above, this divergence from the age criteria was unlikely to make a substantive difference to the analysis results. The CALIMA study included patients on medium dose ICS as well as those on high dose ICS. However, medium dose ICS was excluded from the MAIC analysis, so as to correspond to the target population.

The population for which NICE recommendation is sought was a subgroup of the overall trial data. Relevant subgroup data were not available for competitor trials. Therefore, "the comparison versus mepolizumab was performed in the full trial populations for benralizumab and mepolizumab" (CS, Section B.3.3.2.2, p.172). The ERG noted that that MAIC analysis had not been conducted in the population for which NICE recommendations is sought. This adds uncertainty regarding the accuracy and applicability of the MAIC results in the CS, which contributed to the economic model.

In response to this issue, AstraZeneca made an assumption that "We consider it reasonable to assume that the relative efficacy between the drugs will be the same in the all-comers trial population as in the more severe sub-group; and we have not identified any reasons/clinical rationale against this assumption" (CS Section B.3.3.2.2, p.172). However, as discussed earlier, and supported by clinical advisor to the ERG, David Halpin, benralizumab has a fundamentally different mechanism of action than mepolizumab. Therefore, it did not seem reasonable to the ERG to assume in the absence of data that the relative efficacy between

the all-comers population and the more severe sub-group would be equal for benralizumab and mepolizumab.

The consequences of this decision on the analysis were unknown. The ERG asked AstraZeneca for further clarification on their decision (ERG's clarification question, A8). In response, AstraZeneca said that they validated this assumption with a UK clinician and found "no evidence to the contrary". They also stated that this approach was taken in the appraisals for mepolizumab and reslizumab against omalizumab. Indeed, omalizumab has a very different mechanism of action from mepolizumab and reslizumab. AstraZeneca therefore said that "We therefore believe that this is the most methodologically sound approach in the absence of further evidence, given that both treatments are more efficacious in the more severe subgroup". The ERG still believe this to be a very strong assumption, since, while both treatments are more efficacious in the more severe subgroup, they may not be more efficacious by the same amount. Moreover, the ERG could not find any evidence to quantify any difference in the relative treatment effect between benralizumab and mepolizumab according to severity.

4.4.7 Results of base case MAIC analysis

4.4.7.1 Exacerbation trials (SIROCCO/CALIMA versus MENSA/DREAM)

[redacted] 45 [redacted]

[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]

[redacted] 13 [redacted]

14

15

4.4.7.2. OCS sparing trials (ZONDA versus SIRIUS)

[redacted]46[redacted]

[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]16[redacted]

[redacted]17[redacted]

[redacted]

[redacted] 18

[redacted]

[redacted]

[redacted]

4.4.8 Results of MAIC scenario analysis for exacerbation trials including MUSCA trial

[redacted] 47

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted] 48

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted] 19 [redacted]

The figures above showed that in both MUSCA scenario analyses, after matching,

4.4.9 Overall comment on the MAIC analysis

Indirect treatment comparison using anchored MAIC was largely conducted following relevant NICE DSU 18 and NICE Working Guide recommendations. The results of the base case MAIC showed

There were some areas of concern, among which the ERG judged the most important to be:

- Evidence of selective outcome reporting, whereby outcomes were not reported in the CS or considered as clinical inputs to the economic model
- The effect modifier selection process for the MAIC analysis excluded effect modifiers that were not in imbalance between the benralizumab and mepolizumab trials contrary to NICE DSU recommendations
- The MAIC analysis comparing benralizumab and mepolizumab was conducted in the full trial population rather than the subgroup for which NICE recommendation was sought
- Imputation of data from one technology to another despite benralizumab having a fundamentally different mechanism of action from mepolizumab and reslizumab. No clinical analysis was conducted to compare benralizumab and reslizumab – instead clinical equivalency was assumed. The relative efficacy of benralizumab and mepolizumab between the more severe sub-group and the all-comers trial population was assumed to be equivalent. Neither of these assumptions was evidence based.

- The exclusion of the MUSCA trial appeared contrary to the inclusion criteria, and when this study was included in the MAIC analysis comparing benralizumab with mepolizumab, [redacted]

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness could be undertaken by the ERG. Since a considerable proportion of the data upon which the CS was based are unpublished, the ERG requested IPD (ERG's Clarification question to company, B1). IPD would have allowed the ERG to check the clinical analyses. However, AstraZeneca declined (Company response to clarification question, B1) to provide IPD within the time frame of the appraisal.

4.6 Conclusions of the clinical effectiveness section

From the pooled subgroup analysis of SIROCCO/CALIMA based on population per NICE scope, benralizumab demonstrated a significant reduction in the annual asthma exacerbation by 53% (RR = 0.47; 95% CI 0.32 – 0.67: p < 0.001) and [redacted] The reduction in AER for the pooled subgroup analysis was similar to that from the ITT analysis of the SIROCCO trial (51%) but higher than the AER reduction from the ITT analysis of the CALIMA trial (28%). Rate of exacerbation associated with ER visits was also reduced by 69% (RR = 0.31; 95% CI 0.09 – 1.01: p = 0.51) but not with hospitalisation (RR = 1.01; 95% CI 0.30 – 3.45: p = 0.988), in the pooled analysis.

[redacted]

Benralizumab improved lung function FEV_1 pre-bronchodilator change from baseline by 254mls (95% CI 113mls to 395mls) and reduced ACQ-6 score for asthma control by -0.43 (95% CI -0.69 to -0.16), compared to placebo. Improvement in asthma control was not clinically important. Benralizumab also improved EQ-5D-5L-assessed quality of life by 0.04 (95% CI 0.01-0.08; p = 0.019) compared to placebo. Asthma-related quality of life was unavailable for the pooled subgroup but

[redacted]

The beneficial effect of Benralizumab on annual asthma exacerbation appeared consistent in both pooled trials only for the Asian population. No death was considered related to investigational product.

While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the

[redacted]

Benralizumab appears to be well tolerated with an adequate safety profile in the short term (up to one year). The most common reported side effects include worsening asthma, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis although these occurred at similar rates compared to placebo

The ERG noted that the adequate safety profile obtained from the CS pivotal RCTs was based on trial data with patients concurrently treated with oral corticosteroids. The ERG noted that the CS did not look to include observational studies assessing safety of benralizumab.

While no cases of anaphylaxis were observed in SIROCCO or CALIMA, the ERG noted that patients were excluded from SIROCCO and CALIMA trials if they had a history of anaphylaxis with any biologic drug. It has been reported in the literature that anaphylaxis may occur rarely (0.3%) after exposure to reslizumab and the ERG suggest further studies are needed to establish risk of anaphylaxis for benralizumab for people with no prior exposure to any biologic drug.

Future surveillance studies are needed to establish the risks of benralizumab on malignancy and safety in the medium to long term as well as during pregnancy.

The MAIC analysis was largely conducted according to NICE DSU recommendations. However, AstraZeneca declined the ERG's request to provide IPD within the time frame of the appraisal, precluding the ERG from checking the clinical analysis which incorporated a considerable amount of unpublished data.

Moreover, the ERG had some concerns about the methodology of the MAIC analysis. There was evidence of selective outcome reporting, whereby outcomes for [redacted] were not reported in the CS or considered as clinical inputs to the economic model. The effect modifier selection process for the MAIC analysis excluded effect modifiers that were not in imbalance between the benralizumab and mepolizumab trials contrary to NICE DSU recommendations. Data were imputed from one technology to another despite benralizumab having a fundamentally different mechanism of action from mepolizumab and reslizumab. No clinical analysis was conducted to compare benralizumab and reslizumab – instead clinical equivalency was assumed. The relative efficacy of benralizumab and mepolizumab between the more severe sub-group and the all-comers trial population was assumed to be equivalent. Neither of these assumptions was evidence based.

5 Cost-effectiveness

5.1 ERG's comment on the company's review of cost-effectiveness evidence

5.1.1 Objective

The company conducted systematic literature reviews for published cost-effectiveness studies, quality-of-life data, and costs associated with treatment of severe asthma.

5.1.2 Inclusion/exclusion criteria

Eligibility criteria used in the study selection are shown in Table 49.

Table 49 Eligibility criteria for the systematic review of cost effectiveness

Criteria	Inclusion criteria
Population	Adults, children and young people aged ≥12 years with severe asthma Disease severity classified according to validated criteria (e.g. the Global Initiative for Asthma [GINA] criteria)
Intervention	Benralizumab Reslizumab Mepolizumab Omalizumab No restriction on dose or duration of treatment or use of concomitant best supportive care
Outcomes	Main outcomes, to include: Incremental costs-effectiveness ratio (ICER): Cost per quality-adjusted life year (QALY) ICER: Cost per disability-adjusted life year (DALY) ICER: Cost per event avoided Additional outcomes: Range of ICERs as per sensitivity analyses Assumptions underpinning model structures Key costs drivers Sources of clinical, cost and quality of life inputs Discounting of costs and health outcomes Model summary and structure
Study design	Cost-utility analyses Cost-effectiveness analyses Cost-benefit analyses Cost-minimisation analyses
Territory of interest	No restriction
Date of publication	2012 onwards

Criteria	Inclusion criteria
Language of publication	English language publications or foreign language publications with an English abstract

These searches took a similar format to the clinical effectiveness searches but without the RCT filter and with a cost effectiveness filter. It is unclear which cost effectiveness filter has been used as this has not been referenced and is not one that we recognise. It is unclear why a validated search filter was not used. Embase and Medline were searched separately (which is good practice) using the Ovid platform. Titles of included and excluded papers for the systematic review are not listed. Data extraction methods for included papers are not detailed.

The ERG noted that the systematic literature reviews for quality of life data, and costs were well conducted and reported.

AstraZeneca did not undertake separate literature searches to identify studies reporting adverse events. The company stated that adverse event literature would be best identified in the systematic review of clinical effectiveness literature searches.

AstraZeneca's searches were limited by study design. It is therefore possible that exclusion of cohort, case-control, cross-sectional and case series as publication types in the literature searches (due to the use of an RCT filter) means that papers reporting adverse events may have been missed.

5.1.3 Results

Fourteen cost-effectiveness studies relevant to the decision problem were included.

5.1.4 Conclusions

No economic analyses of the cost-effectiveness of benralizumab as add-on therapy to high-dose ICS/LABA were identified in SLR. Therefore, in order to assess the cost-effectiveness of add-on benralizumab treatment, the company created a de novo economic model, based on a Markov structure.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

The ERG used the NICE reference case checklist in order to assess whether the company model adhered to NICE recommendations. The checklist is shown in Table 50.

Table 50 NICE reference case checklist

NICE reference case requirement	Condition satisfied?	Comments
Decision problem: as per the scope developed by NICE	Yes	Patient population is adults with severe eosinophilic asthma
Comparators: As listed in the scope developed by NICE	Yes	Comparators are SOC, add-on mepolizumab and add-on reslizumab
Perspective on costs: NHS and PSS	Yes	
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	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Systematic reviews were conducted for cost-effectiveness studies, costs, and utilities.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	A lifetime horizon is used
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	EQ-5D-5L and AQLQ were measured directly and mapped onto EQ-5D-3L

NICE reference case requirement	Condition satisfied?	Comments
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	Original UK value set and 5L-3L crosswalk value sets were used
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% p.a. for costs and health effects	Yes	

5.2.2 Model structure

The company submitted an economic model to assess the cost effectiveness of benralizumab as an add-on treatment to SOC, relative to SOC alone, add-on reslizumab, and add-on mepolizumab. The model follows a Markov structure. The ERG noted that the model structure depicted in the model file (

Figure 20) differs from the model structure depicted in the CS report (Figure 21). In particular, no all-cause mortality state is included in

Figure 20, whilst the exacerbation state in Figure 21 is divided into two separate exacerbation states. These exacerbation states are differentiated by the state of asthma that the patient came from (either controlled or uncontrolled). The actual model more closely corresponds to

Figure 20, though is missing the fact that each exacerbation state is comprised of three different types, and is missing the all-cause mortality state. The ERG also noted that there is an error in Figure **21** that suggests it is possible to move from all-cause mortality to an exacerbation state. This error was not reflected in the model implementation.

Each exacerbation state has different implications for costs and utilities, depending on which of the following three treatments are required:

- OCS burst
- ER visit

- Hospital admission

Figure 20 Model structure as reported in company model file

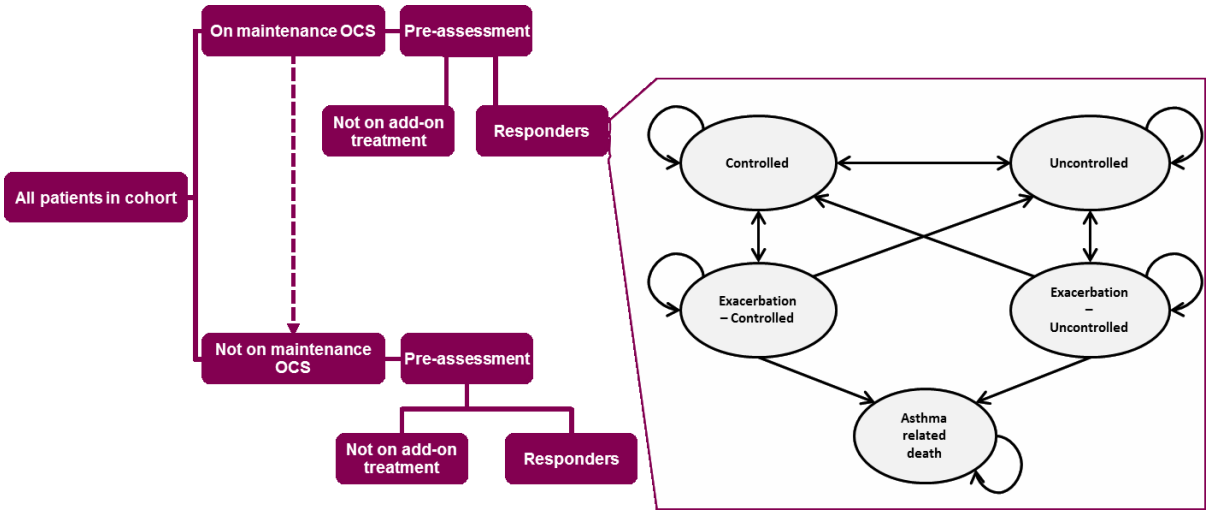
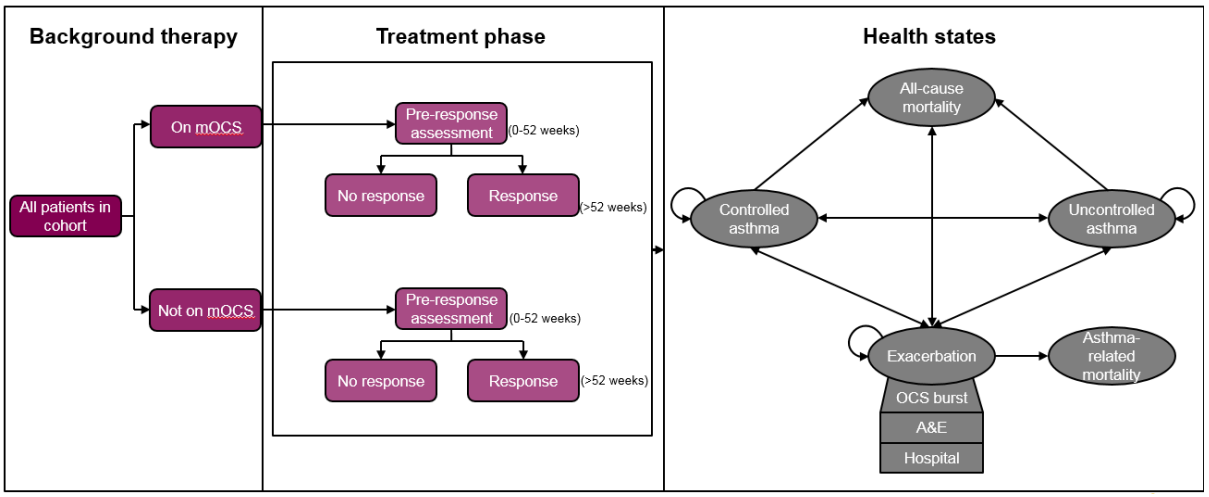


Figure 21 **Model structure as reported in company submission report**



Cycles were 2 weeks in length. This differed from the 4-week cycles used in the appraisals for mepolizumab and reslizumab, but was consistent with the frequency of measurement in the pivotal trials used by the company. The first cycle was counted as a half-cycle (1 week long), and so subsequent cycles fell on odd-numbered weeks.

An exacerbation was defined as lasting for 8 weeks in total, a duration which the company determined via visual inspection of pooled utility data from SIROCCO/CALIMA in order to cover the length of time taken for utility to return to pre-exacerbation levels [11, 12]. The ERG asked the company for clarification about the details of the visual inspection method, as it was not clear from the CS. The company responded that no systematic method had

been used, and accepted that the estimated duration for an exacerbation may vary depending on the reviewer (see Sections 5.2.6.1.2 and 5.2.7.2 for further details).

A description of the model from the ERG's perspective is given as follows, based on Figure 20, which more closely corresponds to the actual model as was implemented. First, patients in the target population being considered were separated into two groups, based on whether they are currently taking mOCS. The model assumed that even if patients were not on mOCS in any given state, they will still be subject to the transition probabilities, costs, and utilities associated with having received mOCS treatment if they were in the mOCS group at baseline. After the assessment point for OCS sparing is reached (set at 28 weeks in the model based on ZONDA trial data) [13], there will also be some movement of patients from the chronic OCS users group to the no chronic OCS users group.

Within each group, add-on treatment is started and continued for the duration of the pre-response assessment period (set at 52 weeks in the base case based on CALIMA and SIROCCO trials) [11, 12]. At the beginning of treatment, all patients were assumed to start in a state of uncontrolled asthma, which was in line with the inclusion criteria in the CALIMA/SIROCCO trials [11, 12]. They can move to either an exacerbated state (Exacerbation – Uncontrolled in

Figure **20**), or the controlled asthma state. Further transitions were depicted as in the grey Markov section of

Figure 20, though the ERG note that *all-cause mortality is possible from any state*, despite not being explicitly shown as such in

Figure **20**.

Once the end of the pre-assessment period was reached, patients who did not respond to treatment were reverted back to SOC, without any additional biologic treatment. The remaining responders continued to receive add-on biologic treatment for life. Mortality of the entire cohort was achieved at the 1302nd cycle. Costs and QALYs were applied to each cycle, and aggregated to provide overall costs and QALYs for cost effectiveness analyses.

In terms of the Markov structure, the ERG noted that a key difference between the model developed for the NICE health technology appraisal for reslizumab and that for benralizumab is that the two exacerbation states in the reslizumab model corresponded to 'moderate exacerbation' and 'severe exacerbation', rather than 'exacerbation – controlled' and 'exacerbation – uncontrolled'. This meant that in the reslizumab model, patients could transition from any asthma state to any exacerbation state. In contrast, in the benralizumab model, there was only one exacerbation state from each origin (controlled and uncontrolled). This meant it was not possible to transition between different severities of exacerbation.

Table 38 of the CS stated that this simplification followed clinical expert opinion that the difference between a moderate exacerbation and uncontrolled asthma would be imperceptible.

No treatment waning effect was incorporated into the model (see Section 5.2.6.4 for further details).

The ERG noted that there was a large discrepancy between the model diagram used in the company's report, and the diagram used in the model. This discrepancy added ambiguity and difficulty in interpreting the model structure, though it was deemed to be internally consistent.

The ERG believe that the model structure was generally appropriate for the economic evaluation and consistent with the asthma clinical pathway.

5.2.2.1 Assessment of response to treatment

The company stated that treatment response was assessed based on a clinically meaningful reduction in the number of exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control after 52 weeks of treatment; these criteria were used in the reslizumab NICE STA [8] and were "aligned to clinical expert preference on the definition and time point" (Table 38, CS). The ERG, however, could not verify and critique these model assumptions since the information on treatment response criteria in the appraisal documents for reslizumab STA was marked as confidential [8].

As the ERG noted in the reslizumab and mepolizumab FADs, treatment stopping rules for these treatments should be implemented at 12 months after the start of treatment, and treatment response should be reassessed each year. It was also emphasized in committee papers for the reslizumab appraisal [8] that in clinical practice, patients are usually reassessed for response on a yearly basis.

The ERG noted that this appeared to differ slightly from the CS for reslizumab. On p.185 of the CS for reslizumab, it was stated that patients are assessed every year, and that patients who remain in uncontrolled or exacerbation states for one year will discontinue treatment.

In the AstraZeneca model, treatment response was evaluated 52 weeks after treatment initiation but it was not reassessed on a yearly basis. In addition to treatment discontinuation at 52 weeks from treatment initiation, the company implemented treatment attrition via a risk of treatment discontinuation applied to each model cycle in every health state (see the next section for further details).

The company stated that [redacted] and [redacted] of patients on mOCS and not on mOCS, respectively, met treatment continuation criteria in the pivotal trials. Since the ERG did not have access to IPD from the trials (see the company's response in Section 5.2.6.1), these estimates could not be verified.

Importantly, the ICER for the comparison versus SOC was very sensitive to this assumption.

In the comparison versus MEPO, the relevant proportions are shown in Table 51.

Table 51 Company's assumption on the percentage of patients responding to benralizumab and mepolizumab in BEN vs. MEPO comparison

	Population	Responders	Non-Responders
Benralizumab	Non OCS	[redacted]	[redacted]
	mOCS	[redacted]	[redacted]
Mepolizumab	Non OCS	[redacted]	[redacted]
	mOCS	[redacted]	[redacted]

* As no information is available for the percentage of patients responding to mepolizumab in the mOCS population, this is assumed to be equal to that of benralizumab

The company stated in the factual accuracy check pro forma: "*The final guidance for mepolizumab states that patients should "continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control." This is the continuation criteria used within the company model and the [redacted] of patients who respond to mepolizumab is reflective of this.*"

The CS reads: "*As the data regarding the percentage of patients responding to mepolizumab is not specific as to whether it applies to the non mOCS or the mOCS population and it is referenced to the MENSA/DREAM trials it is assumed that this percentage relates to the non mOCS population and an assumption is made that the percentage of responders in the mOCS population is equal that of benralizumab.*"

The company stated tin the CS that "*Given the response assessments for reslizumab and benralizumab are the same and that the clinical inputs for the two products are also the same, it is reasonable therefore to assume that the same percentage of patients will respond to each medicine*." Therefore, percentage of patients responding to biologic therapy, benralizumab (mOCS subgroup) and reslizumab, were assumed to be the same, [redacted].

Of note, in RESLI appraisal, this information was confidential. The ERG was concerned with this assumption since BEN and RESLI have different mechanisms of action, and therefore this assumption would need further clarification.

5.2.2.1.1 Treatment discontinuation (attrition) rate

The company assumed that each year 11.8% of patients discontinue treatments with the biologics due to adverse events, personal or physician's preference. It was stated in the CS that the discontinuation rate was sourced from clinical trial data and assumed to be the same for each add-on biologic, as per the precedent set in the recent NICE STA for mepolizumab (TA 431 [7]). Table 52 outlines proportions of patients who withdrew from treatment in the pivotal trials; and the relevant transition probabilities per model cycle along with the probability used in the company's model.

Table 52 Treatment discontinuation in patients with baseline blood eosinophils of >=300/mL

	% patients who withdrew from the study	Length of the study period	Discontinuation probability per model cycle (of 2 weeks)
SIROCCO	[redacted]	48 weeks	0.0049
CALIMA	[redacted]	56 weeks	0.0036
ZONDA	[redacted]	28 weeks	0.0037
Company's model	11.8	1 year	0.0048

[1] SIROCCO CSR (p84)
[2] CALIMA CSR (p 80)
[3] ZONDA CSR (p77). Of note, Table 11.1.1.2 in the ZONDA CSR (reporting the profile of patients disposition for patients with baseline blood eosinophils of >=300/mL) was referenced but was not included in the document. The company states in the CSR (p74) that the proportion of patients who withdrew from the study was similar across subgroups.

In the MEPO appraisal, the annual attrition rate was assumed to be 10% (p. 81, committee papers dated 1 December, 2016).

When the average discontinuation probability of 0.0041 estimated from the pivotal trials (Table 52) was assumed in the company's model, the ICER for BEN vs. SOC increased only slightly (by ~£100 per QALY gained). This change did not affect qualitatively the result for the comparisons against MEPO. However, when the PAS for MEPO was applied, the ICER increased moderately.

The ERG examined the appropriateness of applying a constant probability or treatment discontinuation. Our clinical expert advised us that this assumption is relevant to the clinical practice.

The ERG believe that it would not be unreasonable to assume that some patients would return to treatment after discontinuation. As such, the overall discontinuation rate may be lower.

In the base case, the ERG applied the average discontinuation rate from the pivotal trials via the probability of attrition of 0.0041 per model cycle; this constituted *Item 5* of the ERG's base case (Section 5.3.1).

This change has virtually no effect on the company's base-case results. Under the PAS discount for MEPO, however, the decrease in the attrition rate moderately increases the relevant ICER.

5.2.3 Population, Interventions, and Comparators

The CS provided base case results for the cost effectiveness of benralizumab as an add-on treatment to SOC, relative to:

1. SOC only
2. Mepolizumab + SOC
3. Reslizumab + SOC

5.2.3.1 Patient populations for different comparisons

According to the NICE scope, the patient population in this appraisal is adults with severe asthma with elevated blood eosinophils. However, the company is seeking a NICE recommendation for the subgroup of patients detailed in the first column of Table 53 since analyses of the pivotal trials demonstrated that BEN is particularly effective in patients from this subpopulation. This patient population was considered in the cost-effectiveness analysis of BEN vs. SOC only. The comparisons against the biologic drugs, MEPO and RESLI, were conducted in different populations which were in line with the NICE recommendations for MEPO and RESLI (Table 53).

Table 53 Patient populations considered in the company's economic analyses

Base Case Population (BEN vs. SOC)	**Mepolizumab NICE recommended population (BEN vs. MEPO) [7]**	**Reslizumab NICE recommended population (BEN vs. RESLI) [8]**
A NICE recommendation is sought for adults with severe eosinophilic asthma that is inadequately controlled,	NICE recommends mepolizumab in a sub-population of the licensed indication:	*"Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe*

Base Case Population (BEN vs. SOC)	Mepolizumab NICE recommended population (BEN vs. MEPO) [7]	Reslizumab NICE recommended population (BEN vs. RESLI) [8]
despite high-dose inhaled corticosteroids (ICS) (≥ 800µg FP daily) plus long acting β-agonists (LABA) with: *A blood eosinophil count that has been recorded as 300 cells per microlitre or more* *AND either* *3 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months* *OR* *Treatment with continuous oral corticosteroids over the previous 6 months*	*"Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:* *the blood eosinophil count is 300 cells per microlitre or more in the previous 12 months and* *the person has agreed to and followed the optimised standard treatment plan and* *has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or* *has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months"*	*eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:* - *the blood eosinophil count has been recorded as 400 cells per microlitre or more* - *the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months"*

Based on clinical advice, the target population of ≥300 eosinophil cells per µl seems reasonable as a population threshold for treatment with IL-5 related drugs, as well as the additional population requirements: ≥3 exacerbations needing systemic corticosteroids in previous year, or mOCS over previous 6 months.

The ERG agreed that the model populations for the comparisons between BEN vs. MEPO, and BEN vs. RESLI should take into consideration the patient populations in the respective NICE guidances.

5.2.3.2 Patient characteristics

Table 54 shows patient characteristics assumed in the company's model along with those reported in the CSRs for the pivotal trials.

Table 54 Patient characteristics

Characteristic	Value assumed in the company's model[1]			Pooled data from SIROCCO and CALIMA[2], mean (SD)		Values reported in sources, mean (SD)	ERG's base case
	BEN vs. SOC	BEN vs. MEPO	BEN vs. RESLI	BEN (N=123)	Placebo (N=136)		
Age, years	50.2	49.8	50.2	50.8 (11.5)	49.6 (12.7)	[redacted] 51(11.3)[5] 44.9 (13.7)[6]	As in the CS
Weight, kg	NA	NA	75.2	NR	NR	[redacted] 83.1 (19.7) [5] 81.2 (19.9)[6]	Weight distribution from Haselkorn et al. (2009) [10]
Female, %	64.5 %[1]	66.1%[1]	63.3%[1]	60.2[2]	68.4[2]	63.1[6]	As in the CS
% patients on mOCS at baseline	54.1 % (DOF)	78.6% (DOF)	0% RESLI (TA479) [8]	23.6[2]	23.5[2]	15.7%[7]; [redacted] 41.7%[6]; 16.5% in patients 18-64 y.o. (n=313) and 17.1% in patients >=65 y.o. (n=168) (Kerkhof et al., 2017)[8]	41.7% (as in Heaney et al., 2010 [5])

[1] baseline characteristics from pooled data on 259 patients from SIROCCO and CALIMA (Section B.3.3.1, CS, p164)
[2] Table 22, CS
[3] based on the subpopulation of patients of 12 - 75 years old with baseline blood eosinophils of >=300/mL (SIROCCO CSR), % of 12-18 y.o. patients was 3.3%
[4] based on the subpopulation of patients of 12 - 75 years old with baseline blood eosinophils of >=300/mL (CALIMA CSR), % of 12-18 y.o. patients was 2.2%
[5] estimated from full analysis set for adult patients (N=220) from ZONDA trial
[6] cross-sectional data from a UK registry on 382 UK adult patients with difficult asthma defined as "persistent symptoms and/or frequent exacerbation despite treatment at step 4/5 of British Thoracic Society (BTS) management guidelines", *mean eosinophil count at baseline was 0.3 x 10^9 (0.25-11.0)* (Heaney et al. (2010) [5]
[7] Table 15 (p. 109), SIROCCO CSR
[8] UK patient population with severe uncontrolled eosinophilic asthma defined as patients receiving high-dosage ICS plus LABA in both baseline and outcome years, had 2 or more attacks in the baseline year and had a high blood *eosinophil count of >=300 per µL* at index date (Table 2, Kerkhof et al., 2017 [6])
DOF, data on file; NR, not reported

5.2.3.2.1 Mean weight of patients with severe asthma

The company did not report the mean weight of patients from the pooled SIROCCO/CALIMA data set. The company modelled the mean weight of 75.2 kg reported in the appraisal of reslizumab [8]; this estimate was based on 3082 and 3083 trials. Importantly, this assumption affected BEN vs. RESLI comparison only, as RESLI dose is based on patient's weight (see Section 5.2.8.1.3 for further details).

The mean weight in Heaney et al. (2010) [5] was 81.2 (SD=19.9) kg (Table 54) which is substantially higher than in the company's model. The mean weight of adult patients in ZONDA trial was 83.1 kg (Table 54). Our clinical expert confirmed that a subgroup of patients with severe asthma have a high body mass index (BMI).

Therefore, the company's assumption on patients' weight does not accurately reflect clinical experience. In the ERG's base case, a weight distribution in severe asthma patients was modelled together with the vial-based dosing scheme for RESLI [9] (see Section5.2.8.1.3).

5.2.3.2.2 Mean age at treatment initiation

The company stated that the mean age of patients in their base-case analyses was based on pooled data from SIROCCO and CALIMA (see Table 54). The company assumed the mean age of patients at the start of model simulation of 50.2 years for BEN vs. SOC and BEN vs. RESLI comparisons, and 49.8 years for the comparison of BEN vs. MEPO. These values were rounded down to the nearest whole year in the model, though this was not explicitly stated in the company report.

The age estimate of 50.2 was the average over the BEN and placebo treatment arms in the pooled data (Table 54). However, it was not clear from the CS whether the pooled data represent adult patients only. The company wrote in their response to a clarification question:

"The adolescent patients across both benralizumab and mepolizumab trials comprised <5% of the trial population (MEPO: MENSA-4%, DREAM: <1% (1 patient); BENRA: SIROCCO: 4.4%, CALIMA: 2.3% in high dose group). As the included studies enrolled a very small number of adolescent patients, these studies were considered as representative of adult patients only."

The mean age of patients with baseline blood eosinophils >=300/mL, reported in the CSR for SIROCCO (p96), was 48.5 years; and 49.4 years in CALIMA CSR (p94). Importantly, those estimates were based on the subpopulation of patients of 12 - 75 years old.

The average age of UK adult patients with difficult asthma from a UK registry, reported by Heaney et al. (2010) [5], was 44.9 years (see Table 54). Our clinical expert, David Halpin, confirmed that in clinical practice patients with severe asthma are often younger.

The ERG was aware that in NICE's technology appraisal guidance on omalizumab for asthma [26], the results were based on a weighted average of the ICERs for different age cohorts to reflect different mortality risk by age. Since age is an important driver in this model, the ERG believe that the approach taken in the omalizumab appraisal would produce a more accurate estimate of the cost-effectiveness of benralizumab.

In the base case, the ERG adopted the company's assumption on the mean age of 50.2 years for consistency with the clinical effectiveness data from the pivotal trials on which the company's analysis was based (see Section5.3.1), and the mean age of 44.9 years (as in the UK registry) was assumed in a scenario analysis (see Section 5.2.9.2.3).

5.2.3.2.3 Proportion of female patients

The ERG considered the higher proportion of females observed in the submission's three pivotal trial populations (approximately 65%) as a reasonable reflection of clinical practice.

5.2.3.2.4 Proportion of patients on mOCS at baseline

In the company's model, 54.1% and 78.6% of patients were assumed to take mOCS in BEN vs. SOC and BEN vs. MEPO, respectively; in the BEN vs. RESLI comparison it was assumed that no patients take mOCS. The proportions for benralizumab and mepolizumab were based on trial data. The reslizumab figure was taken from the reslizumab STA.

It was stated in the NICE committee papers for reslizumab appraisal dated 3rd February, 2017 [8], that "about 50% of patients on what was previously known as steps 4 and 5 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network guidelines are being treated with maintenance oral corticosteroids, but still have several exacerbations" (p. 9, committee papers dated 3 February, 2017) [8].

Based on data from a UK registry of patients with difficult to control asthma (Heaney et al., 2010) [5], 41.7% of such patients use mOCS (see Table 54). This estimate was for patients with a *mean* eosinophil count at baseline of 0.3 x 10^9 (0.25-11.0). Kerkhof et al. (2017) [6] reported mOCS use in ~17% of UK patients with severe uncontrolled eosinophilic asthma with *eosinophil count of >=300 cells per µL* (see Table 54). Therefore, the ERG believe that the modelled proportions of patients taking mOCS at baseline did not reflect UK clinical practice.

When a rate of 41.7% reported by Heaney et al. (2010) [5] was assumed for the BEN vs. SOC comparison in the company's model, the ICER increased to £36,546 per QALY gained.

The rate of 17% reported by Kerkhof resulted in the ICER of £41,976 per QALY for this comparison. These rates had no effect on the qualitative result for the BEN vs. MEPO comparison.

The rate from Heaney et al. (2010) [5] was used in the ERG's main analysis. This assumption constituted *Item 2* of the ERG's base case (Section 5.3.1).

The estimate reported in Kerkhof et al. (2017) [6] was assumed in a scenario analysis conducted by the ERG (Section 5.3.2.3).

5.2.4 Interventions and comparators

Based on clinical advice, any patients currently receiving SOC would only be those who do not need anti-IL5 therapy. About 90% of anti-IL5 therapy requiring patients would receive mepolizumab, and only a minority (up to 5%) would receive reslizumab principally because of the intravenous route of administration. A small percentage of patients needing anti-IL5 therapy may continue on SOC for logistical reasons or personal choice. These percentages are likely to remain the same in the next 2 years because of the issue of giving reslizumab intravenously. Therefore, the ERG considered MEPO as the major comparator in this appraisal.

5.2.5 Perspective, time horizon and discounting

The model was costed from the perspective of the NHS in the UK. The time horizon for the add-on treatment is lifetime, given a response to the add-on biologic treatment is achieved after the assessment period of 52 weeks. Otherwise, SOC treatment continues (without an add-on biologic) for the remainder of life. Both costs and utilities are discounted at a rate of 3.5%. These model assumptions are in line with the NICE Guidance [17].

5.2.6 Treatment effectiveness and extrapolation

The main sources of treatment effectiveness data for benralizumab and SOC are the three pivotal trials CALIMA, SIROCCO, and ZONDA [11-13]. Given that CALIMA and SIROCCO involved the same benralizumab treatment programme, and measured similar key outcome variables, data from both of these studies were pooled to provide a more powerful indication of treatment effectiveness.

Apart from the proportion of responders to treatment for mepolizumab, all other clinical inputs were assumed to be the same across add-on treatments. This included the annual risk of discontinuation (11.8%) and the response assessment threshold (52 weeks). The ERG note that there is an error in Table 72 of the CS, where the probability of discontinuation per cycle is stated incorrectly as 0.0044, as opposed to the correct value

0.0048. However, the correct value has been used in the model, and so there is no impact on the reported ICERs.

The level of adherence to add-on treatment was assumed to be 100% for all three biologics. This assumption is consistent with the STAs for reslizumab and mepolizumab. The CS states that this is a conservative assumption as it is likely to overstate drug costs. The ERG noted that it may also affect health-related quality of life estimates generated by the model. Nevertheless, it represents a reasonable assumption for a model of this nature.

Clinical inputs for reslizumab were assumed to be equivalent to benralizumab. This is because the company determined that a MAIC could not be conducted between the two treatments, due to significant differences between the trials.

5.2.6.1 Transition probabilities

Transition probabilities between Markov states for benralizumab were derived from the 2-weekly ACQ-6 scores in the SIROCCO and CALIMA (pooled), and ZONDA trials [11-13]. For the base case, transition probabilities for those not on mOCS were computed using pooled SIROCCO/CALIMA data, limited to those ≥18 years of age, using 800ug ICS fluticasone equivalent per day, having an eosinophil count of greater than or equal to 300 cells per μL and having experienced 3 exacerbations or more in the preceding year. Assessment of treatment response was made at 52 weeks, based on observation of a 'clinically meaningful reduction in the number of exacerbations needing systemic corticosteroids'.

Since exacerbation states were deemed to last 8 weeks, the transition probabilities of entering an exacerbation state are 4 times higher than the actual probability. This reflects the fact that transition probabilities used in the model must be in accordance with a 2-week cycle length.

For those receiving mOCS at baseline, patient level data from the ZONDA trial was used to calculate transition probabilities. The analysis was limited to patients ≥18 years of age and having an eosinophil count of ≥300 cells per μL.

The transition probabilities for mepolizumab were calculated using results from the MAIC analysis in the full trial populations for mepolizumab and benralizumab, but applied to the NICE recommended population for mepolizumab (see Section 4.4.7 for further details on the MAIC analysis).

AstraZeneca stated:

"In the absence of a head to head trial between benralizumab and mepolizumab an indirect comparison was assessed for feasibility, however, due to there being no published data from mepolizumab in the mepolizumab NICE recommended population the only possible indirect comparison is between the full trial populations."

The rate ratios for annualised rate of clinically significant exacerbations for add-on benralizumab vs. mepolizumab were 0.94 for those not on mOCS, and 0.56 for those on mOCS. The exacerbation rate for mepolizumab was calculated by taking the reciprocal of these rate ratios, and multiplying this by the exacerbation rate found in the benralizumab arm of the three pivotal trials.

Treatment responsiveness for mepolizumab was obtained from the mepolizumab NICE STA data. The proportion of responders was assumed to only hold for non-mOCS users (76.7%), since it was not specified in the STA report which population the response proportions applied to. The proportion of responders for the mOCS population on mepolizumab was, therefore, assumed to be the same as the proportion of responders for benralizumab (77.05%).

Transition probabilities for reslizumab were assumed to be identical to benralizumab, as no additional data were available (a MAIC analysis between benralizumab and reslizumab was deemed to be unsuitable). As a result of this, all other clinical values were also deemed to be identical between benralizumab and reslizumab. This includes exacerbation rates, and the proportion of responders to the treatment. The ERG noted that this may not be realistic in practice, due to differences in biological action between the two treatments. The comparison between benralizumab and reslizumab is only conducted on non-mOCS users, due to a lack of data and the fact that mOCS users were not included in the NICE recommendation for reslizumab.

Given that no treatment data after 52 weeks were available, the CS used the imputed transition probabilities for responders within the duration of the trial in order to calculate transition probabilities in the model for responders to the add-on treatment after the initial 52-week pre-assessment period.

AstraZeneca stated that:

"We consider it reasonable to assume that the relative efficacy between the drugs will be the same in the all-comers trial population as in the more severe sub-group; and we have not identified any reasons/clinical rationale against this assumption."

However, a clinical advisor to the ERG expressed concern about this assumption.

The distribution of individuals in each of the three exacerbation states was derived from pooled SIROCCO/CALIMA data (non-mOCS users) and ZONDA (mOCS users). The distributions obtained for benralizumab were used for all add-on treatments.

The ERG had concerns over the explanation of derivation of transition probabilities in the CS. The company stated in the CS that "Exacerbation rates, quality of life and transition probabilities were derived from three benralizumab trials, a pooled analysis of CALIMA and SIROCCO for patients not on mOCS (published and *unpublished* data) and ZONDA for patients who are on mOCS". The ERG requested individual patient data (IPD) used in these analyses. The company wrote in their response dated 19 February, 2018:

"In relation to the request for individual patient data, AstraZeneca would consider undertaking further analyses with the provision of a protocol and statistical analyses plan, and may consider providing the data if appropriate and after guarantee of safeguarding of the de-identified and anonymised patient data. It should be noted that it is estimated that a request for access to IPD may take several months to action due to internal governance processes."

Since IPD was not provided by AstraZeneca, the ERG could not validate the treatment effectiveness analysis conducted by the company. However, the ERG believe that the health state transition probabilities used in the company's analysis could not be robust given the relatively small sample sizes used to obtain those estimates (Table 55), a relatively low exacerbation rate in severe asthma patients (about one exacerbation per year), and 4 x 4 (four-by-four) transition probability matrices (shown in Appendix 4).

Table 55 Number of patients in different analyses of transition probabilities

BEN vs	Non mOCS			mOCS		
	BEN		Comparator	BEN		Comparator
	transition probabilities in weeks 0-52	transition probabilities in weeks >52		transition probabilities in weeks 0-52	transition probabilities in weeks >52	
SOC	123[1]	104[2]	136[1]	61[3]	47[4]	64[3]
MEPO	Based on the whole trial *non mOCS* population[5]			Based on the whole trial mOCS population		
RES	123	100[5]	As for BEN	The comparison in mOCS patients was not performed.		

[1] SIROCCO/CALIMA
[2] estimated by the ERG (assuming that [redacted] of patients were responders as stated in the CS) since the company did not provide the number of patients in this analysis
[3] ZONDA
[4] estimated by the ERG (assuming that [redacted] of patients were responders as stated in the CS) since the company did not provide the number of patients in this analysis
[5] MAIC results for SIROCCO/CALIMA versus MENSA/DREAM
[6] MAIC results for ZONDA versus SIRIUS

[5] estimated by the ERG (assuming that [redacted] of patients were responders as stated in the CS) since the company did not provide the number of patients in this analysis

5.2.6.1.1 Controlled and Uncontrolled Asthma

The Controlled and Uncontrolled model health states were determined using the ACQ-6 score at the end of each 2-week cycle as described in Section 5.2.8.4.

5.2.6.1.2 Exacerbations

The company wrote: "Given that exacerbations are assessed over an 8-week period, while asthma control and transition to exacerbations are assessed on a 2-weekly basis, the transition probability matrix based on 2-weekly model cycle interpretation reflects a 4 times higher than actual probability of entering an exacerbation state that lasts 4 times shorter than the actual length of time in that state. This means that model calculations track patients to enter 2 weekly exacerbations states 4 times repeatedly, resulting an exacerbation duration of 8 weeks in line with the trial data." (CS p167).

Exacerbation rates

During each model cycle, patients may experience one of the three types of clinically significant exacerbations: exacerbations requiring treatment with OCS, exacerbations treated in ER, and exacerbations treated in hospital. The modelled frequency of exacerbations, and the severity of exacerbations (in terms of the frequency of hospitalisations) were derived from the SIROCCO/CALIMA (pooled) and ZONDA trials.

The company estimated the percentage (%) of each type of exacerbation (see Table 56) by taking the number of exacerbations in each treatment group and dividing it by the total number of exacerbations.

Table 56 Exacerbation distribution extracted from pooled clinical trial data, Base Case population

Parameter	N	%	Source
Controlled			
Benralizumab - mOCS			
OCS treated exacerbations	3	100	ZONDA
Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Benralizumab - Non mOCS			
OCS treated exacerbations	16	100	SIROCCO/CALIMA

Parameter	N	%	Source
Exacerbations treated in the ER	0	0	SIROCCO/CALIMA
Exacerbations treated in hospital	0	0	SIROCCO/CALIMA
Uncontrolled			
Benralizumab - mOCS			
OCS treated exacerbations	13	100	ZONDA
Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Benralizumab - Non mOCS			
OCS treated exacerbations	22	81.48	SIROCCO/CALIMA
Exacerbations treated in the ER	0	0	SIROCCO/CALIMA
Exacerbations treated in hospital	5	18.52	SIROCCO/CALIMA
Controlled			
Standard Care - mOCS			
OCS treated exacerbations	21	100	ZONDA
Exacerbations treated in the ER	0	0	ZONDA
Exacerbations treated in hospital	0	0	ZONDA
Standard Care - Non mOCS			
OCS treated exacerbations	25	89.29	SIROCCO/CALIMA
Exacerbations treated in the ER	1	3.57	SIROCCO/CALIMA
Exacerbations treated in hospital	2	7.14	SIROCCO/CALIMA
Uncontrolled			
Standard Care - mOCS			
OCS treated exacerbations	31	68.89	ZONDA
Exacerbations treated in the ER	5	11.11	ZONDA
Exacerbations treated in hospital	9	20	ZONDA
Standard Care - Non mOCS			
OCS treated exacerbations	99	85.34	SIROCCO/CALIMA
Exacerbations treated in the ER	9	7.75	SIROCCO/CALIMA

Parameter	N	%	Source
Exacerbations treated in hospital	8	6.91	SIROCCO/CALIMA

Source: Table 69 (p180, CS)
'mOCS use' and 'non mOCS' use refer to use of mOCS as part of baseline therapy.

These exacerbation rates were used for the whole duration of treatment. It was assumed that those patients, who did not meet treatment continuation criteria and discontinued BEN, experience exacerbations at the same rate as patients treated with SOC.

For the comparisons of benralizumab versus other biologics, the company assumed that the split of exacerbations is the same for all comparators, by applying the split for benralizumab patients to mepolizumab and reslizumab patients. The ERG believe that this is one of the most stringent assumptions in the CS. As noted earlier, benralizumab has a different mechanism of action compared to mepolizumab.

The number of exacerbations of different types per person per year predicted by the company's model are detailed in Table 57; these were derived by averaging the total number of exacerbations suffered by the model population over model time horizon.

Table 57 Average number of exacerbations per person per year from the company's model

Comparison	Treatment	OCS burst	ER	Hospitalisation
BEN vs. SOC	BEN	0.8420268	0	0.04662142
	SOC	0.88107409	0.06889393	0.1036128
BEN vs. MEPO	BEN	0.95886164	0	0.02828311
	MEPO	0.97282891	0	0.02821356
BEN vs. RES	BEN	0.66262923	0	0.10095661
	RES	0.66262923	0	0.10095661

The ERG noted that model predictions for the BEN vs. MEPO comparison in Table 57 are in line with the results of the MAIC analysis reported in [redacted].

As for the comparison versus RESLI (assuming the same effectiveness for BEN and RESLI), the predicted exacerbation rates were the same across the treatments.

Exacerbation rates in SIROCCO and CALIMA

Fitzgerald et al. (2016) reported that 51% of placebo patients (126 out of 248) had >=1 exacerbations during 56 weeks trial period, the total number of exacerbations was 270, resulting in 1.09 exacerbations per placebo patient per 56 weeks. Only 8% of all exacerbations in the CALIMA trial led to either ED visit or hospitalisation in the placebo arm.

The rate of 0.68 exacerbations per patient receiving BEN Q8W was reported in Fitzgerald et al. (2016), and as in placebo arm, 8% of all exacerbations resulted in ED visit or hospitalisation.

In SIROCCO trial, the annual exacerbation rate in placebo and BEN Q8W patients was 1.53 and 0.66, respectively; 14% of all exacerbations required an ED visit or hospitalisation over the trial period of 48 weeks versus only 7% of patients on BEN Q8W.

Table 58 Annual exacerbation rate associated with ED visit or hospitalisation for patients receiving high dosage ICS plus LABA with baseline blood eosinophils >=300 cells per millilitre

Trial	Placebo	BEN Q8W	Source
SIROCCO	14% (based on data from 37 patients)	7% (based on data from 18 patients)	Bleecker et al. (2016) [11], Appendix 14, Table 3 (estimated over 48 weeks)
CALIMA	8% (based on data from 20 patients)	8% (based on data from 20 patients)	Fitzgerald et al. (2016) [12], Appendix 14, Table 3 (estimated over 56 weeks)

Hospitalisation rate by geographic region

Importantly, percentage of exacerbations leading to hospitalisation in SIROCCO trial differed substantially in patients from the base-case population residing in Europe and Eastern Europe, 18% and 42%, respectively. Asthma hospitalisation rate in Eastern European patients was also substantially higher in CALIMA trial. Of note, patients from Eastern Europe constituted ~31% of the total population in the SIROCCO trial, and ~36% in the CALIMA trial.

Therefore, the ERG believe that hospitalisation rates were overestimated in the CS since about 1/3 of all patients in the pivotal trials were from Eastern Europe, where asthma-related hospitalisation was about 40% higher than in Western European countries. Therefore, the difference in costs of treating exacerbations in patients on OCS and biologics could be at least partly a result of the regional differences.

Table 59 Exacerbations leading to hospitalisation in previous 12 months by geographic region for patients receiving high dosage ICS plus LABA with baseline blood eosinophils >=300 cells per millilitre

Trial	Eastern Europe	Western Europe	Asia	North America	South America	Source
SIROCCO (N=809)	42% (n=250)	18% (n=164)	17% (n=96)	20% (n=142)	15% (n=157)	Bleecker et al. (2016) [11], Appendix 17, Table 5
CALIMA (N=728)	31% (n=259)	11%(n=102)	8% (n=72)	11% (n=128)	11% (n=167)	Fitzgerald et al. (2016) [12], Appendix 18, Table 6

Since the IPD used to estimate transition probabilities and exacerbation rates were not provided by AstraZeneca, the ERG could not critique these model assumptions.

5.2.6.2 mOCS consequences

The company commissioned a matched historical cohort study using the Optimum Patient Care Research Database (OPCRD), and the Clinical Practice Research Datalink (CPRD) database, in order to measure the negative impact of mOCS use. Based on this study, the prevalence/incidence of 10 comorbidities as a result of mOCS use were obtained for each daily dose level. These were then used to compute costs and disutilities from OCS use in the model.

5.2.6.3 Steroid sparing effect

Complete and partial mOCS sparing proportions were assessed at baseline and at 28 weeks in the ZONDA trial, by the daily dose level of mOCS taken. The mOCS sparing level for mepolizumab was calculated using results from the MAIC analysis.

For the comparison vs. SOC, the company assumed that 30.1% and 10.7% of patients in the BEN and SOC arms, respectively, discontinue mOCS at 28 weeks after treatment initiation. In the MEPO comparison, the respective proportions for BEN and MEPO were 20.2% and 9.82%; these proportions were not reported in the company's submission (they were taken from the company's model).

The ERG noted that there is a typographical error in Table 70 of the CS, where the daily dose category of '5 - <7.5' is incorrectly labelled as '6 - <7.5'.

In MEPO appraisal, to account for benefits of mOCS sparing, the company applied a reduction of £4,000-£9,000 to the ICER in a scenario analysis, referring to the appraisal of omalizumab (p. 133, committee papers dated 1 December, 2016).

In the RESLI appraisal, the model did not incorporate stopping or reducing the dose of oral corticosteroids, because the dose was kept constant in the pivotal trials (p. 13, committee papers dated 3 February, 2017) [8].

5.2.6.4 Treatment waning effect

The company did not model treatment waning effect since they found "no evidence of treatment effect waning"; it was also stated that this assumption is "consistent with other appraisals in the disease area" (Table 38, CS). No additional analysis of the kind was provided by AstraZeneca.

Based on clinical advice, the ERG believe that this assumption is reasonable. However, according to the Guide to the Methods of Technology Appraisal, additional analyses "assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions" should be conducted [17]. Also, the Appraisal Committee for mepolizumab appraisal considered that a scenario analysis exploring a waning effect would be valuable (p. 100, committee papers dated 8 June, 2016 [7]). Such scenario analyses were conducted by ScHARR, the ERG for the mepolizumab appraisal; they predicted substantially higher ICERs compared to those assuming no waning effect. Therefore, the ERG believe that further analysis with respect to this assumption would be appropriate.

5.2.6.5 Mortality in asthma patients

AstraZeneca assumed in their model that patients may die of asthma as well as of other causes, therefore both asthma-induced and all-cause mortality were incorporated into the model. In both cases, the company used age-dependent probabilities of death. The AZ model predicted 1.5 times higher mortality in patients from the population of interest compared to the UK general population of the same age.

The ERG was advised by the clinical expert, David Halpin, that deaths due to asthma in people *who are concordant with appropriate therapy* are relatively uncommon. Based on the clinical advice and recent asthma mortality data, the ERG believe that mortality was overestimated in the company's model. A critique of the company's view in relation to modelling mortality is provided below.

5.2.6.5.1 Background mortality

The rates of all-cause mortality in the company's analyses were taken from UK National Life Tables for 2012–2014 and applied to all transitions in the model. The ERG noted that more recent life tables for 2014-16 are now available.

Asthma-related mortality was not removed from all-cause mortality as *the relatively small number of asthma deaths* was considered unlikely to materially impact the results, i.e. all patients in all health states in the company's model experienced all-cause mortality, and both all-cause and asthma-related mortality were applied together in the exacerbation states.

In the additional analysis conducted by the ERG, the UK National Life Tables for 2014-2016 were used [46]. This change, however, had a minor effect on the results. Therefore, the ERG did not include this change in the base case.

5.2.6.5.2 Asthma-related mortality

In previous economic evaluations relevant to this appraisal (i.e. of mepolizumab, reslizumab, and omalizumab) asthma-related mortality was identified as one of the key drivers of the cost-effectiveness of the treatments.

No deaths due to asthma were observed in the pivotal trials. Therefore, probabilities of asthma-related mortality were estimated from alternative published sources. The company conducted a literature review of asthma-related mortality to identify UK studies reporting mortality rates as a result of severe asthma, or risk factors for asthma-related death. The company noted that data on mortality from Watson 2007, Roberts 2013 and the NRAD report [3] were used in the base-case analysis. However, no further details related to the literature review was provided in the CS.

In the model, the company assumed that a patient could die from asthma only after a clinically significant exacerbation. For exacerbations requiring a hospital admission, the model uses mortality data from Watson et al. (2007) combined with Roberts et al. (2013) and for exacerbations not requiring a hospital admission (i.e. OCS burst and ER visits) from Watson et al. (2007) combined with locations from the National Review for Asthma Deaths (NRAD) [2, 1, 3]. This approach was consistent with the method used in the mepolizumab NICE STA (TA431) [7].

Deriving probabilities of death given an exacerbation treated by an OCS burst or an A+E visit

Watson et al. reported mortality incidence, stratified by age, within an acute severe asthma population following a hospital admission in 2000-2005. However, this does not provide estimates for the probability of death for an exacerbation treated with either an OCS burst or an A+E visit. Therefore, for exacerbations not requiring a hospital admission (i.e. OCS burst and A+E visits) the data were combined with the results from the NRAD and the percentage of each type of exacerbation from the SIROCCO/CALIMA trials as outlined in Table 60 and Appendix 1. The NRAD report only provides the percentage of deaths which occur from each type of exacerbation, however, the trial data shows that certain types of exacerbation are more frequent than others. A detailed account on how the probabilities of asthma-related death were derived is presented in Appendix 1.

Table 60 Asthma exacerbation-related mortality inputs used in the base case model

	AstraZeneca (base case)		ERG's base case
Age band (years)	**Probability of death**	**Data source: Watson et al. 2007, Roberts et al. 2013, NRAD 2014 [2, 1, 3]**	
OCS burst			
17 – 44	0.000501	Watson et al. + NRAD	0.000200*
45 – 100	0.003240	Watson et al. + NRAD	As in the CS
ER visit			
17 – 44	0.003165	Watson et al. + NRAD	0.001266*
45 – 100	0.020475	Watson et al. + NRAD	As in the CS
Hospital admission			
18-24	0.0015		0.0006*
25 – 34	0.0014	Roberts et al.	0.00056*
35-44	0.0020		0.0008*
45 – 54	0.00756	Watson et al. fitted to Roberts et al.	*0.003024**
55 – 64	0.02142	Watson et al. fitted to Roberts et al.	*0.018144**
65 – 100	0.04536	Watson et al. fitted to Roberts et al.	As in the CS

Source: Table 79 of CS (p190)
The age band 17-44 is used in the DSA and PSA only
* derived by dividing the company's probability by 2.5

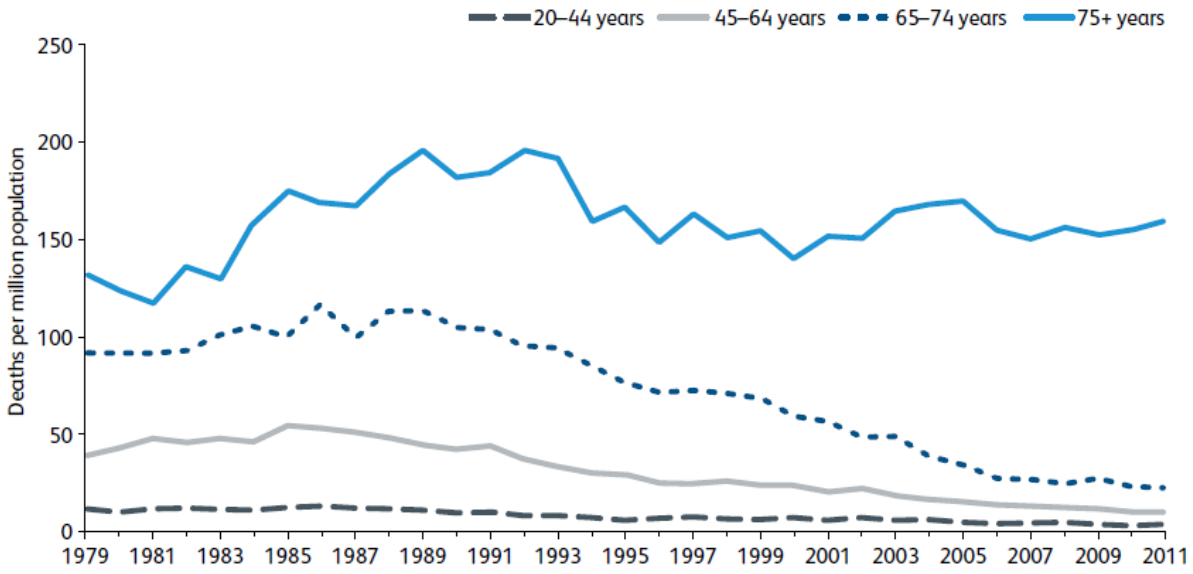
The impact of these assumptions was explored by AZ in a scenario analysis where asthma related mortality was set to zero. The ICER for comparison vs. SOC increased from £34,284 (base case) to £67,260 per QALY.

The NRAD [3], which the company referred to in their submission, reported asthma deaths occurring between February 2012 and January 2013 in the UK; 195 people died of asthma in this period, including *61 people with severe asthma*. About 45% of people "were known to have died *without seeking medical assistance* or before emergency medical care could be provided".

The ERG performed an ad hoc search for literature on asthma mortality in UK patients. According to the most recent source identified during the search, BTS adult asthma audit report (2016) [4], there were "*33 deaths* reported *following hospital admission* with acute asthma in this audit" of 4258 UK *adult* patients in 2016. This results in the average probability of death of 0.0078 per hospital admission.

The weighted average of the probabilities of asthma death in hospital, used in the company's base case (Table 79, p190, CS), is 0.01943. It is ~2.5 higher than the estimate of 0.0078 based on the BTS adult asthma audit report (2016) [4].

Figure 22 Death attributable to asthma (males and females of 20+ years combined), UK 1979-2011



Source: the NRAD report [3], Fig. 1.2

Figure 22 shows changes in the number of asthma-attributable death in UK adults in 1979-2011. Importantly, the number of asthma deaths in the UK recorded in 2011 decreased substantially when compared to the time periods covered by Watson and Roberts, 2000-2005 and 1981-2009, respectively. As shown in Figure 22, asthma deaths reduced during 1979-2011 in all age categories except 75+; the number of deaths in this age category changed during this period rather irregularly.

As clearly seen in Figure 22, asthma-related deaths increase markedly after the age of 74. Given the significant increase in mortality observed starting from age 75, the ERG believe that assuming the same mortality risk in 65+ patients who were hospitalised for asthma may produce favourable cost-effectiveness results to benralizumab.

Deaths in patients requiring an OCS burst or ER visit, was modelled even in broader age groups, 17-44 and 45-100 (Table 60).

The ERG believe that it would be more appropriate to model mortality in narrower age categories especially in older patients.

In the ERG's analysis, it was assumed that probabilities related to asthma-induced death for patients up to the age of 45 for OCS burst and ER visit, and up to the age of 65 for hospital admission are 2.5 times lower than in the company's base-case (see Table 60).

No adjustments were applied to the death rates in 45-100 y.o. (for OCS burst and ER visit) and 65-100 y.o. (for hospitalisation) as it was not possible to conduct extensive searches for relevant sources due to time constraints.

Importantly, *only adjustments made to 45-54 and 55-64 age categories for hospital admissions were effectively used in the ERG's base case* since the modelled age at treatment initiation was 50 years.

In the updated base case for the MEPO appraisal, mortality rates in hospitalised patients from these age categories were 0.0092 and 0.0152, respectively; the probability of death in patients 65+ was 0.0455 (p. 75, committee papers dated 1 December, 2016).

In RESLI appraisal, the asthma mortality was modelled based on Roberts et al. (2013) [2] (p. 32, committee papers dated 20 July, 2017). The authors reported odds ratio estimates from a logistic regression model for asthma-related mortality *within 30 days from hospital admission for asthma.* The following odds ratio estimates were used:

- 2.4 for 45-54 age group

- 6.3 for 55-64 age category

- 12.3 for 65+ patients

The 18-24 age group was the reference category.

Predicted patient survival in the company's and the ERG's base case analyses is shown in Table 61 Model predictions of life expectancy in asthma patients (years)Table 61.

Table 61 Model predictions of life expectancy in asthma patients (years)

	Asthma-related probabilities of death as in the company's base case	Asthma-related probabilities of death as in the ERG's base case	UK life expectancy for 50-years-old person*
BEN	78.7**	81**	83.1
MEPO	78	80.1	
RES	77.2***	81.8***	
SOC	77.3	80.4	

* weighted average assuming 64.5% female as in the CS base case
** base-case population
** reslizumab population

Under the company's base-case assumption on the risk of asthma mortality, life expectancy of patients treated with BEN is 78.7 years; patients on MEPO survive for 78 years; RESLI patients for 77.2 and patients on standard-of care treatment are predicted to live for 77.3 years.

In the ERG's base case, survival is slightly higher in all patients (see Table 61) but still lower than the UK life expectancy of 83.1 years in people aged 50. This estimate represents a weighted average of survival across genders, assuming 64.5% are female (as in the company's model).

When the reduced probabilities of asthma-related death (Table 60) were applied to the company's model, the ICER for BEN vs. SOC increased by more than £2,000.

The estimate based on BTS adult asthma audit report (Scott et al., 2017 [4]) was used in the ERG's additional analyses; this constituted *Item 1* of the ERG's base case (Section 5.3.1).

5.2.7 Health related quality of life

A systematic literature review was conducted to identify HRQoL and utility studies relevant to the decision problem. In the searches, 24 studies were identified. Utility values from one of the studies, Lloyd et al. (2007) [16], were considered in scenario analyses conducted by the company. The ERG noted that these estimates related to patients with a diagnosis of moderate or severe asthma (BTS level 4 or 5).

5.2.7.1 Health states' utilities

Health state utilities were obtained from two different measures: the EQ-5D-5L, and AQLQ(S)+12 (an asthma-specific quality of life measure). Both measures were collected in the SIROCCO and CALIMA trials, whilst only the AQLQ(S)+12 was collected in the ZONDA trial [11-13]. The EQ-5D-5L was measured weekly, and reflects quality of life at time of

measurement. The AQLQ(S)+12, however, was only measured every 4 weeks, where each measurement reflects quality of life in the previous 2 weeks.

Both measures were mapped onto EQ-5D-3L. In the pooled SIROCCO/CALIMA data, EQ-5D-3L utility scores were estimated by the 'crosswalk' value set, which is based on 996 randomly selected individuals from England [47]. The AQLQ(S)+12 data were mapped using a regression equation from Tsuchiya et al. [48]. The ERG accepted that whilst a mapping from AQLQ to EQ-5D is likely to be imprecise, the only trial that appears to measure OCS-related utility is ZONDA, which did not measure EQ-5D directly.

The difference between controlled and uncontrolled states in the model was determined by ACQ-6 scores reported by the patient (<1.5 for controlled, ≥1.5 for uncontrolled).

Utility values used in the company's model are shown in Table 62.

Table 62 Utility values used in the company's base case

State	Utility value: mean (SE)
Controlled, non mOCS, benralizumab	0.8689 (0.01793)
Controlled, mOCS, benralizumab	0.8478 (0.00907)
Controlled, mOCS, SOC	0.8562 (0.00994)
Uncontrolled, non mOCS, benralizumab	0.7325 (0.0181)
Uncontrolled, non mOCS, SOC	0.7010 (0.0167)
Uncontrolled, mOCS, benralizumab	0.7364 (0.0165)
Uncontrolled, mOCS, SOC	0.6977 (0.01368)
Exacerbation, OCS or A+E prior HS Controlled, non mOCS	0.8209 (0.03732)
Exacerbation, OCS or A+E prior HS Controlled, mOCS	0.8189 (0.02638)
Exacerbation OCS or A+E, prior HS Uncontrolled, non mOCS	0.7157 (0.02678)
Exacerbation, OCS or A+E prior HS Uncontrolled, mOCS	0.6545 (0.01931)
Exacerbation, Hospitalised	0.6413 (0.05285)

HS: health state

The company stated that the integrated safety summary showed similar incidence of AEs for the placebo group (77.6%) compared with the benralizumab (74.7%) group. Therefore, no

adverse events were included in the company's model because of small proportions and minor differences between treatment groups.

The ERG considered the approach undertaken by AstraZeneca appropriate as the evidence came from the pivotal trials. The ERG requested IPD to verify the utility values used in the CS. The requested data, however, was not provided by AstraZeneca (see the company's response in Section 5.2.6.1). Therefore, the health state utility values used in the company's model could not be verified by the ERG.

Of note, in the RESLI appraisal, utilities reported by Willson et al. (2014) [49] and Lloyd et al. (2007) [16] were used.

5.2.7.2 Disutilities of exacerbations

The duration of disutility of exacerbations assumed in the company's model, was based on an analysis by Golam et al. (2017). The ERG noted that this study was funded by AstraZeneca.

The methodology used in Golam et al. (2017) is explained below.

It was found in the analysis that an exacerbation impacts a patient's utility over the periods outlined below:

- OCS: 24 days prior to exacerbation start data to 24 days post exacerbation start date (7 weeks in total)
- ER: 31 days prior to exacerbation start data to 31 days post exacerbation start date (9 weeks in total)
- HOSP: 31 days prior to exacerbation start data to 38 days post exacerbation start date (10 weeks in total)

In the company's base case, the duration of disutility of exacerbations of *any type* was assumed to be 8 weeks (or 4 model cycles).

The company provided the graph from Golam et al. (2017) (see Figure 23), which shows the 'grand mean' utilities and the 'mean of averages' utilities for each type of exacerbation. The company set week 0 as the start of the exacerbation. They chose the start point of an exacerbation as:

> *"…the point where the weekly utility started to decline (closest week for which the utility weekly value is smaller than the utility weekly value for the week before)."*

Figure 23 Utilities from the company's submission

A 'Grand mean' utilities; B) 'mean of averages' utilities

Table 63 Duration of exacerbations selected by company from Figure 23

Type of exacerbation	Start/end weeks from 'grand mean'	Start/end weeks from 'mean of averages'
OCS burst	-3, +3	-3, +3
ER/ED visit	-4, +4	-4, +4
Hospitalisation	-3, +6	-3, +5

This process was repeated to obtain the end point of the exacerbation (i.e. the end point is the first week after week 0 where the utility is larger than the following week). The start and end points selected by the company are shown in Table 63. From these time spans, the company decided to use 8 weeks as the duration of an exacerbation. The ERG understood that this follows from the visual inspection method described in section 5.2.2 of this report.

The ERG believe that when applying this methodology to Table 63, one would likely extend the duration of an exacerbation beyond what may be reasonable. This is particularly true for exacerbations requiring hospitalisation, whose end point occurs when utility is close to or greater than at any point before the exacerbation.

Furthermore, in Table 83 of the CS, the final collapsed categorisation of health states (Set 3) does not appear to contain different exacerbation states depending on whether the patient came from a controlled or uncontrolled state. The ERG believe that this may be related to

the inconsistency in the model description and its implementation (described in section 5.2.2).

In the model, utilities for the "Exacerbation" health state were computed as a weighted average of the utilities for the three types of exacerbations, i.e. exacerbations requiring OCS burst, ER visit and hospitalisation. Importantly, the company assumed that OCS burst and ER visit have the same impact on patients' quality of life, and therefore the relevant utilities were assumed to be the same. A separate weighted average was calculated depending on the previous asthma state (controlled/uncontrolled), and previous chronic OCS use (Table 62).

In the company's response to clarification questions, their statistical analysis plan stated that only utilities for exacerbations that require an OCS burst will be assessed, due to limited utility data in the ZONDA trial. This may result in the utility from an exacerbation to be overestimated.

The loss in utility due to hospitalisation, assumed during 8 weeks' period, does not reflect recent data from the BTS adult asthma audit report (2016) [4], where the mean length of asthma-related hospital stay was 3 days in the UK in 2016, with a significant number of patients discharged within 24 hours.

Also, in the appraisal of mepolizumab, the duration of utility decrement due to exacerbations requiring OCS burst, ER visit, and hospitalisation were 13 days, 10 days, and 21 days, respectively (MENZA trial). In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) (p. 10, committee papers dated 1 December, 2016).

In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely less than the model cycle of *4 weeks* (p. 57, committee papers dated 20 July, 2017).

Therefore, the ERG believe that durations of disutilities substantially shorter than those assumed by the company would be more plausible; they would lead to a higher ICER for the comparison versus MEPO and SOC.

In addition to health state utilities, the model incorporated disutilities suffered as a result of chronic mOCS use: "The long-term utility loss due to conditions and AEs as a consequence of mOCS use was captured by calculating 2 weekly disutility values from the annual disutility values reported in Sullivan et al. [50]. These values were applied by combining data from the ZONDA trial, data provided by the Observational & Pragmatic Research Institute (OPRI) and condition-specific disutility values from Sullivan et al" (CS, p 205).

The ERG requested all the data on health-related quality-of-life used in the company's analysis. AstraZeneca wrote in their response that *"all health-related quality of life data used in this context was taken from the Sullivan paper and has been provided as a reference. No analyses on HRQoL for the adverse events associated with maintenance OCS use have been performed by AstraZeneca."*

Ten different adverse events from mOCS use from Sullivan et al. [50] were considered. For renal impairment and pneumonia, 'other diseases of kidney and ureters' and 'lung diseases due to external agents' were used as proxies due to a lack of data. These were combined into a weighted average of disutilities based on prevalence/incidence and the percentage of patients within each mOCS daily dose band. The percentage of patients within each dose band differed between baseline and at 28 weeks (the end of the ZONDA trial). Therefore, in the model, the percentage of patients in each band at baseline was used to calculate disutility in the initial 28-week period. After this, the percentage of patients in each band at 28 weeks was used to calculate disutility. The overall disutility from mOCS use was set to 0 in one scenario analysis.

5.2.8 Resources and costs

The company undertook a systematic literature review in order to identify relevant health and resource utilisation costs; 32 cost studies were selected.

5.2.8.1 Drug acquisition

5.2.8.1.1 Wastage

It was not clear from the CS whether the assumption of full wastage was implemented. The ERG followed advice from the clinical expert, David Halpin, assuming no vial sharing in all additional analyses.

5.2.8.1.2 SOC

SOC was derived from the key pivotal trials and defined as high dose ICS/LABA. This was costed using relative market shares (IMS) of all ICS/LABA combinations based on BNF prices 2017. A summary is provided in Appendix 2. Note that ICS and LABA were recorded in the trial as separates but were costed to reflect clinical practice – use of combination ICS/LABA therapy as directed by the BTS/SIGN guidelines. High dose was defined as at least 800ug fluticasone equivalent.

The average cost of SOC is based on high dose ICS/LABA (at least 800µg fluticasone equivalent). The cycle cost of £21.21 used in the model represents an average of the available ICS/LABA combinations based on BNF 2017 prices, weighted by the market share

of each drug. The ERG's clinical expert agreed that this was a sensible method to estimate the cost of SOC.

5.2.8.1.3 Biological drugs

Intervention and active comparator drug costs are shown in Table 64 and Table 65. SOC is part of each treatment considered in this appraisal and therefore was not costed. In the main analysis, unit costs of biologics were based on the PAS price for benralizumab, and the list prices for mepolizumab and reslizumab reported in the British National Formulary. The costs per 2-week model cycle were calculated for each add-on treatment, based on these prices (Table 64).

The ERG found that in Tables 89 and 90 of the CS, the strength of add-on benralizumab is given as 100mg, though the dose administered in the trials was 30mg. However, Table 1 in Document A of the CS states the price is for 30mg. The ERG believe this is likely to represent a typographical error in Document B of the CS.

Table 64 Unit costs associated with the technology in the company's model

Medicine	Strength	Cost/Unit	Source
Add-on benralizumab[1]	100mg	List: £[redacted] PAS Price: £[redacted]	AstraZeneca
Add-on mepolizumab	100mg	List: £840	BNF [51]
Add-on reslizumab	2.5ml (25mg)	List: £124.99	BNF [51]
	10ml (100mg)	List: £499.99	BNF [51]

[1] Benralizumab solution for injection is supplied in a sterile single-use prefilled syringe for individual use
Source: Table 89 (p. 249, CS)

Table 65 Cycle costs associated with the technology in the company's model

Medicine	Strength	Cost/Cycle	Source
Add-on benralizumab	100mg	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca
Add-on mepolizumab	100mg	£420	BNF [51]
Add-on reslizumab	2.5ml (25mg)	£62.50	BNF [51]
	10ml (100mg)	£249.99	BNF [51]

The unit cost of benralizumab reflects the cost per 8 weeks (starting from the fourth administration), and therefore was divided by 4 to adjust to the 2-weekly cycle length. Due to the initiation phase of treatment with benralizumab, where benralizumab is injected every 4 weeks for the first 3 applications and then subsequently every 8 weeks, the first year of treatment is more expensive than the subsequent years. Therefore, patients are assumed to receive 8 doses of benralizumab in the first year and 6.5 doses thereafter, cycle costs are calculated accordingly.

The unit cost of mepolizumab reflects the cost per 4-weeks, as it is administered once every four weeks for all patients, the cost is adjusted to the 2-week cycle length.

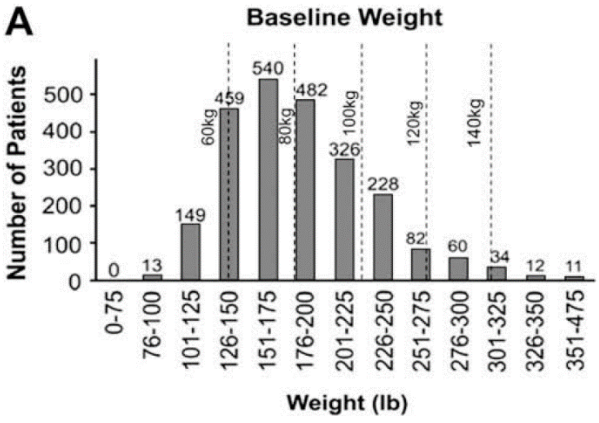
Reslizumab

Reslizumab is administered as an intravenous infusion every 4 weeks. It is available as a 2.5ml or 10ml vial (25mg and 100mg). Dosing of RESLI depends on a patient's weight. The volume (in ml) required is calculated as follows: 0.3 x patient body weight (in kg) [9]. The company stated that per patient cost of reslizumab can range from approximately £6,499.87 per patient per year for a patient weighing between 35-41kg, a 10-ml dose administered every 4 weeks to approximately £37,373.96 per patient per year for a patient weighing between 192-199kg, a 57.5 ml dose (the maximum recommended dose in the SmPC [9]) administered every 4 weeks.

The company estimated the average annual cost per adult patient on add-on reslizumab based on the average patient weight published in the reslizumab NICE STA TA479 of 75.2kg [8]. This average patient would require 22.5 ml of reslizumab at a cost of £1,124.97 per 4 weeks and adjusted to the 2-week cycle length accordingly.

As stated in Section 5.2.3.2.1, the mean weight of 75.2 kg is not representative of UK patients with severe asthma.

Figure 24 Weight distribution (Haselkorn et al., 2009)



Haselkorn et al. (2009) [10] reported an observational study conducted in the US. The mean weight at baseline of 2396 patients with severe asthma was 83.7 kg, 72.2% were female patients, and the mean age of patients was 50 years. This estimate is quite similar to the mean weight of adult patients reported in ZONDA trial, 83.1 kg (see Section 5.2.3.2.1).

In the main analysis, the ERG adopted reslizumab vial-based dosing and wastage based on the weight distribution from Haselkorn et al. (2009) [10]. This assumption constituted *Item 4* of the ERG's base case (Section 5.3.1).

Incorporation of the weight distribution and the vial-based dosing scheme for reslizumab into the company's model improves the cost-effectiveness of benralizumab.

Patient access schemes for mepolizumab and reslizumab

Both mepolizumab and reslizumab have patient access schemes (PASs) agreed with the Department of Health. The PAS discounts are confidential. Therefore, the base-case analyses, conducted by the company for BEN vs. MEPO and BEN vs. RESLI, assumed the list prices for the comparators as per the advice received during the Decision Problem meeting for benralizumab. The company conducted SAs assuming different level of discounts for the comparators. The ERG prepared a confidential appendix with analyses assuming the PASs for BEN, MEPO and RESLI, as these results are the most relevant to the NHS.

5.2.8.2 Tests

The ERG noted that the response to treatment with reslizumab will depend on careful selection of patients with eosinophilic driver to the asthma.The cost of conducting a routine full blood count to identify the persistent eosinophil threshold for potential eligible biologic patients was not included in the company's model under assumption that this is currently conducted at routine attendances for severe asthma patients irrespective of whether they are started on a biologic. This is consistent with previous appraisals for asthma biologics.

5.2.8.3 Drug administration

The company assumed that all administrations for a biologic therapy are undertaken by a specialist asthma nurse. The administration times were taken from the relevant NICE STA publications, see Table 66. The time assumed in the mepolizumab STA included reconstitution time for mepolizumab, and therefore there was an assumption that the administration of benralizumab would take less time as there is no need for reconstitution. SOC was assumed to take no administration time due to it being self-administered.

Table 66 Costs of drug administration in the company's base case and the ERG's base case including monitoring time

	AstraZeneca				ERG
Treatment	**Administration time (mins)**	**Unit cost per hour**	**Cost per administration**	**Source**	
SOC	0	N/A	N/A	Assumption	N/A
BEN	5	£108	£9	Assumption of time saving vs. mepolizumab	£44.64[1] for the first 3 doses, £17.86[1] from dose 4 onward
MEPO	10	£108	£18	Mepolizumab for treating severe refractory eosinophilic asthma (TA431) [7] [52]	£44.64[1] for the first 3 doses, £17.86[1] from dose 4 onward
RESLI	55	£108	£99	Reslizumab for treating severe eosinophilic asthma TA479 [8] [52]	£455[1] for the first 3 visits, £98[1] for the following visits

[1] As in mepolizumab appraisal [7], the costs were inflated to 2018 prices at 3.5% per annum
[2] As in reslizumab appraisal [8], the costs were inflated to 2018 prices at 3.5% per annum
Post-dose monitoring for all biologics was assumed to follow the same protocol in clinical practice

In the company's model, SC administration of mepolizumab takes (on average) 5 mins longer than administration of benralizumab as there is no need for reconstitution of benralizumab. However, based on clinical advice, the reconstitution time for mepolizumab is likely to add a negligible amount of time to overall administration, since it is done during routine nurse interaction with the patient. Therefore, the ERG assumed no difference in the administration time for BEN and MEPO (Table 66).

5.2.8.3.1 Monitoring time after administration of biologics

In clinical practice, drug administration times for the biological treatments include a lengthy (up to two hours) period of supervision, to monitor for anaphylaxis, after the drug has been given. The company did not take this into consideration in their analysis. Therefore, the ERG believe that treatment administration costs for the biological treatments are not reflective of UK clinical practice.

Table 67 Unit cost for administration and monitoring of biologics in the relevant NICE appraisals

Mepolizumab appraisal [7]	Reslizumab appraisal [8]	Omalizumab appraisal [26]
"All administrations for a biologic therapy are undertaken by a specialist asthma nurse, taking 10 minutes of time in total (£16.67, based on a per hour unit cost of £100)" (p. 267, committee papers dated 4 April, 2016). *"Although there is no formal requirement in the draft SmPC, in mepolizumab clinical trial protocols, patients were monitored for one hour following administration"* *£25 (one hour of monitoring, including 15 mins of specialist nurse time).* *Monitoring costs were included up to 16 weeks.*	Three hospital day cases were assumed for the first 3 visits (with the day case admission costs of £316) to account for cannula insertion (£28.50) and increased initial monitoring time (£79.62) with the total administration cost of £108.12. Specialist nurse time was 65 mins from visit 4 onwards resulting in a cost of £63.88; this accounts for the preparation time of 20 mins (committee papers dated 13 February, 2017)	Monitoring costs were included up to and including 16 weeks: 2 hrs for the first 3 administrations, 1 hr from 4th administration to up to 16 weeks. Each hour costing 15 mins of specialist asthma nurse time (p154, ERG's report for omalizumab appraisal)

5.2.8.3.2 Mepolizumab administration

In the mepolizumab appraisal, it was assumed that MEPO administration takes 10 minutes of specialist asthma nurse time (£16.67, based on a per hour unit cost of £100), and that patients are monitored post administration for one hour, including 15 mins of specialist nurse time (i.e. £25 per one hour of monitoring). Monitoring time was costed up to week 16.

5.2.8.3.3 Reslizumab administration

In an additional analysis requested by NICE from Teva Pharmaceuticals for the reslizumab appraisal [8], the administration costs for the first 3 visits for RESLI administration were based on a day-case admission of £316 (HRG code DZ15R), the cost of cannula insertion (£28.50) (Table 69), and increased initial monitoring time (£79.62); the total preparation, administration and monitoring time was assumed to be 80 minutes (including 30 minutes of monitoring).

The HRGs from the National Schedule of Reference Costs 2015-16 which apply to day case treatment of asthma are shown in Table 68.

Table 68 HRG tariffs related to asthma (day case)

Currency Code	Currency Description	National Average Unit Cost
DZ15M	Asthma with Interventions	£753
DZ15N	Asthma without Interventions, with CC Score 9+	£373

Currency Code	Currency Description	National Average Unit Cost
DZ15P	Asthma without Interventions, with CC Score 6-8	£420
DZ15Q	Asthma without Interventions, with CC Score 3-5	£378
DZ15R	Asthma without Interventions, with CC Score 0-2	£367

Source: National Schedule of Reference Costs 2015-16

Table 69 Cost of cannula insertion

Cost item	Cost	Source
Registrar	£10.33	PSSRU – Curtis 2011 – 1 Hour £62
Band 5 nurse – 10 mins	£6.67	PSSRU – Curtis 2011 – 1 Hour £40
Consumables - cannula	£6.97	Consumable costs – see source
Total	£23.97	
Inflated to 2016 at 3.5%	£28.50	

Source: p66 (Reslizumab committee papers dated 3 February, 2017) [8]

From the fourth administration of reslizumab, 65 minutes of specialist nurse time was costed at £63.88, which included 20 minutes of preparation time (p15, Reslizumab committee papers dated 3 February, 2017) [8].

When these assumptions were incorporated into the AstraZeneca model, the ICER for BEN vs. SOC increased by ~£400. As for comparisons with the biologics, these assumptions were less favorable for BEN but did not change the results qualitatively.

The updated administration costs constituted *Item 3* of the ERG's base case (Section 5.3.1).

Two scenario analyses were conducted by the ERG assuming that supervision is required up to 16 weeks after treatment initiation, and for the whole treatment period (Section 5.3.2.3).

5.2.8.4 Health state unit costs and resource use

The company stated that the resource use by health state was calculated using estimates provided in Willson et al. [53, 49] since they considered these sources as most closely aligned with the AZ model structure, and provided UK specific estimates. Willson et al. used data from the PrimoTinA-asthma clinical trial to estimate the resources used by each health state in their model. The model by Willson et al included seven different health states, whereas the number of health states in the AZ model was reduced to four.

First, ‘controlled asthma’ (ACQ < 1) and ‘partly-controlled asthma’ (1 ≤ ACQ < 1.5) were subsumed into one controlled asthma state. Costs for this state were taken as a weighted average of the costs for the two states in Willson et al., with a weight of 0.49 given to those with ACQ < 1, and 0.51 given to those with 1 ≤ ACQ < 1.5. No information appears to have been provided as to the source of these weights, but the ERG found that these were based on trials 3082 and 3083 for reslizumab, as stated in the reslizumab company submission. The ERG considered that it would me more appropriate if the weights were derived from the pivotal trials (CALIMA, SIROCCO, ZONDA).

The, ‘non-severe exacerbation’ state was excluded from the benralizumab model. Finally, ‘severe exacerbation with hospitalisation’ and ‘severe exacerbation without hospitalisation’ were combined into a single exacerbation state. However, it was unclear as to how these were combined to provide a single number of weekly patient visits, as stated in Table 94 of the CS.

Consequently, the levels of resource use reported in Willson et al. were also utilised in the AZ model, with adjusted unit costs.

No medication costs were considered, as the costs of rescue medications and oral corticosteroids were assumed to be negligible compared to other medical costs and due to lack of robust data. The ERG agree with this since those costs would be under £1 per model cycle for all health states. Non-medication costs included inpatient resource use, outpatient visits, home visits, tests and procedures. This information was collected throughout the PrimoTinA trial and in a survey of 15 UK healthcare providers.

In Willson’s study, exacerbation was defined as an acute episode of progressive worsening of at least one asthma symptom outside the usual range of symptoms, lasting for at least 2 days. A severe asthma exacerbation additionally required initiation of treatment with systemic (including oral) glucocorticosteroids for at least 3 days or, in the case of ongoing systemic glucocorticosteroid therapy, requiring at least doubling of previous daily doses for at least 3 days. A severe exacerbation in this study lasted, on average, for 15.1 days (Willson 2014).

The endpoints related to exacerbations, used in the company’s analysis, were from SIROCCO and CALIMA, i.e. asthma exacerbation events treated by:

- OCS burst
- ED visits
- Hospitalisations

Therefore, in the model there was no health state for non-severe exacerbations. Based on the definition of the model health states, no hospitalisations were accounted for in the controlled and uncontrolled health states.

The levels of healthcare resource use for 'Controlled asthma' in the AZ model was calculated using a weighted average of the 'Controlled asthma' and 'Partly controlled asthma' costs from Willson et al.

Table 70 Comparison of health state definitions in Willson et al and the company's model

Willson et al. [49, 53]	Benralizumab Model
Controlled Asthma: ACQ<1	Controlled asthma: Asthma: ACQ <1.5 (weight of 51%) Adequately controlled asthma identified as ACQ <1 (weight of 49%)
Partly-Controlled Asthma: 1≥ ACQ<1.5	
Uncontrolled asthma: ACQ ≥1.5	Uncontrolled asthma: ACQ ≥1.5
Non-severe exacerbation: The symptoms are outside the patient's usual range of day-to-day asthma and last for at least 2 consecutive days, and/or a decrease of PEF of ≥30.	Not Included
Severe exacerbation without hospitalisation: Non-severe exacerbation + corticosteroids (at least 3 days)	Exacerbation
Severe exacerbation with hospitalisation: Severe exacerbation + hospitalisation	

Unit costs were applied to the levels of healthcare resource use estimated by Willson. The mean cost of severe exacerbation was a weighted average of the cost of severe exacerbations leading and not leading to hospitalisation.

In the Willson study, the cycle length of the model was one week. A non-severe exacerbation was assumed to last one week whereas a severe exacerbation (with and without hospitalisation) lasted for 2 weeks. In order to align these health state costs with the model assumption that an exacerbation lasts for 8 weeks and is assigned during 4 different cycles the cost of an exacerbation is divided by 4 to avoid overestimating the true cost of exacerbations. Health state cycle costs and full cycle costs are presented in Appendix 3.

No information was provided in the CS as to how the costs for a nurse visit, and for home visits, were calculated. The ERG was able to reconcile the cost for a nurse visit as 15.5 minutes of nurse time at £43 per hour. This uses the same assumption for visit duration as was used in the reslizumab STA, though it does not appear to be reported as such in the

CS. The ERG believe that the other costs were calculated using information from the reslizumab company submission in a similar way.

The ERG noted that costs for only one type of exacerbation state were stated in the CS, but that two exacerbation states were used in the model (depending on whether the patient came from a controlled state or an uncontrolled state). Therefore, there was an implicit assumption in the model that the cost of an exacerbation does not depend on the previous asthma state, but that utility does.

The ERG also noted that there was a cost associated with 'visit to specialist' that does not have a source in Table 94 of the CS. The relevant cost from Willson et al. 2014 of 'visits to respiratory specialists' is £133.26 [49]. This cost was also used in the STA for reslizumab. However, this does not match the value of £160.32 stated in Table 94. Therefore, it was not clear how this cost has been calculated.

Various hospital-related unit costs were stated as being weighted averages of multiple cost categories found in the NHS reference costs list. However, the ERG could not find a reference in the CS as to which weights were used, or how they were obtained. The ERG verified that the STA for reslizumab used weights based on the number of cases for each category, as reported in the NHS reference costs list from 2014-15. When the ERG applied this same method to the 2015-16 and 2016-17 reference costs, it was unable to reproduce the costs in the CS for benralizumab. For example, based on 2016-17 NHS reference cost data, the ERG calculated that the weighted average cost for 'Asthma exacerbation based hospitalisation' is £1,523 [54]. The health state cost reported in the CS, however, is £2,692.

Other costs have been updated in the latest NHS reference costs list. For example, in the CS, the costs of an ambulance was from NHS reference costs 2015-16 (£96.25). This figure is £98.70, based on 2016-17 data [54].

Due to these discrepancies, the ERG recalculated health state cycle costs. The updated costs are shown in Appendix 3. The health state costs used in the CS and those estimated by the ERG are shown in Table 71.

Table 71 Health state costs per model cycle

Health State	AstraZeneca[1]	ERG[2]
Controlled Asthma	£16.38	£16.42
Uncontrolled Asthma	£53.97	£54.17
Exacerbation	£184.07	£143.23

[1] Table 95, CS
[2] NHS reference costs 2016-17 and Willson 2014) [54, 49]

The updated health state costs increase the base-case ICER for BEN vs. SOC by about £200; the results for the other comparisons do not change qualitatively, i.e. BEN remains dominant. Since the updated costs change ICERs marginally, we do not pursue it further.

5.2.8.5 Costs of adverse events arising from mOCS use

The cost of resources used as a result of comorbidities arising from mOCS use were calculated from the OPRI study. The data from this study was requested by the ERG. For chronic conditions it is assumed that on average, the prevalence is constant throughout the time horizon. For events, annual incidence rates were used.

Ten comorbidities were identified in total. A weighted average of costs by prevalence/incidence of each comorbidity was calculated for each daily dose level of mOCS. This weighted average was then multiplied by the proportion of patients on each daily dose level in order to calculate the overall cost of mOCS use for each dose level. These costs are set to 0 in a scenario analysis.

The ERG noted that whilst the proportion of mOCS users came from the ZONDA trial, an assumption was made in the model in order to compute the proportion of mOCS users on mepolizumab. The assumed figures in the model are stated to have come from the ZONDA trial and MAIC analysis. No reference to the mepolizumab mOCS costs used in the model appears to be contained in the cost section of the CS (B.3.5), even though these are computed and used in the model.

5.2.9 Cost effectiveness results

5.2.9.1 Base case

The base case ICERs reported in the CS are summarised in Table 72.

Table 72 Base case ICERs from CS

Comparator technology	Population	Incremental Costs	Incremental QALYs	ICER per QALY	Matches result in model file?
Add-on Benralizumab vs. SOC	Base case	[redacted]	[redacted]	£34,284	Yes
Add-on benralizumab vs. Add-on mepolizumab	NICE recommended for mepolizumab	[redacted]	[redacted]	Dominant	Yes

Add-on benralizumab vs. Add-on reslizumab	NICE recommended for reslizumab	[redacted]	[redacted]	Dominant	Yes

It should be noted that these base-case ICERs are calculated under the assumption that *benralizumab is provided at the PAS price, whilst mepolizumab and reslizumab are provided at their respective list prices*. This does not reflect the 'true' ICER, which would pertain to PAS prices being used for all three treatments.

Furthermore, quality of life data for reslizumab was assumed to be identical to benralizumab, hence explaining the identical total QALYs between the two treatments. Given differences in the mechanism of action between the two treatments, the ERG noted that this assumption is likely to be unrealistic in practice.

5.2.9.2 Sensitivity analyses

5.2.9.2.1 Deterministic sensitivity analyses (DSAs)

The company undertook two deterministic sensitivity analyses. The first involved a comparison between benralizumab and SOC; the second compared benralizumab to mepolizumab. The CS stated that each parameter included in the analysis was set to the lower and upper limits of its 95% confidence interval (where available). Otherwise, where a confidence interval was not available, the parameter was varied by +/- 20% of the base case value, or "standard upper and lower limits".

The ERG noted that the administration costs for mepolizumab and reslizumab, as well as the health state costs for all four states in the model, were varied by +/- 25%. However, the reason for this is not stated in the CS. This appears inconsistent, particularly since the administration cost for benralizumab was only varied by +/- 20%.

The ERG recalculated the tornado diagrams from the CS, after correcting the aforementioned limits from 25% to 20%. Whilst the comparison with mepolizumab is identical to the CS (Figure 35 and Figure 36 in Appendix 5), health state costs are no longer included in the tornado diagram when benralizumab is compared to SOC (Figure 33 and Figure 34 in Appendix 5).

5.2.9.2.2 Probabilistic sensitivity analyses (PSAs)

The company undertook two PSAs. The first involved a comparison between benralizumab and SOC; the second compared benralizumab to mepolizumab. Each PSA consisted of 1000 simulated draws from distributions. The full list of parameters varied, and their

distributions, can be found in Table 99 of the CS. The ERG replicated these two PSAs and obtained similar results to those found in the CS. The resulting plots are shown in Figure 37, Figure 38, Figure 39, and Figure 40 in Appendix 5. For the comparison vs. SOC, the CS stated that benralizumab produced an additional [redacted] QALYs at an incremental cost of [redacted]. The company states that this generates an ICER of £33,606, whilst in Table 105 of the CS, the ICER is stated as £33,728. The ERG noted that [redacted] = £33,640, so it is likely that one of the aforementioned figures in the CS arises as a result of a rounding error.

For the comparison vs. mepolizumab, the CS stated that benralizumab produced an additional [redacted] QALYs at an incremental cost of [redacted]. This result suggests that benralizumab dominates mepolizumab. The ERG noted that there is a discrepancy between the values stated in text, and Table 106 in the CS [redacted] incremental costs and [redacted] incremental QALYs). Again, this was believed to be due to rounding errors.

To summarise the distributions used: proportions, utilities and disutilities, and mortality rates were drawn from beta distributions (since these variables are constrained between 0 and 1). Response assessments for add-on treatment and steroids, and costs were drawn from gamma distributions. Transition probabilities were drawn from a gamma distribution (with a scaling factor of 1000 applied to the alpha parameter) and then normalised using a Dirichlet process in order to ensure probabilities sum to 1.

The only exceptions to this were: the proportion of OCS users at baseline, % of benralizumab users with complete OCS sparing, and % of standard case users with complete OCS sparing. These three variables, though proportions between 0 and 1, are drawn from gamma distributions.

There were some discrepancies between the information in Table 99 of the CS, and the model file. The exacerbation rates for benralizumab and SOC (of which there are 24 in total) are stated in the CS as being drawn from Dirichlet distributions. However, in the model, they are drawn from Beta distributions. This makes no difference in instances where all exacerbation cases are of one type. However, it means that when exacerbations are split between the three categories (OCS burst, ER visit, Hospital admission), the sum of the proportions is not constrained to 1. Though this is unlikely to substantially change results from the PSA, it may still have some impact.

The ERG also noted that whilst the benralizumab response assessment time was included in the PSA, the mepolizumab response assessment time was not included. Given that both response assessments occur at 52 weeks by default, it will not affect the results obtained in the PSA. However, it may lead to errors if the response assessment times were set differently between treatments.

No PSA was undertaken by the company to compare benralizumab to reslizumab. The CS stated that this was due to the assumption of equal effectiveness between the two add-on treatments. However, in terms of a probabilistic analysis, the ERG believe that this assumption could have been relaxed by drawing utilities for benralizumab and reslizumab independently, but from the same distribution. This would have provided a more realistic picture of the uncertainty around the ICER, since it would almost certainly not be the case in practice that the two treatments have exactly equal effectiveness across multiple cohorts.

5.2.9.2.3 Scenario analyses

The CS reported 5 different scenario analyses as follows:

1. Using alternative sources for Asthma related HRQoL values.
2. Utility values within states is assumed to be equal across treatment arms
3. Removing the risk of Asthma death from an exacerbation
4. Removing the costs associated to the consequences of mOCS; removing the disutilities associated to the consequences of mOCS; removing both the costs and disutilities associated to the consequences of mOCS
5. Varying the confidential discount of mepolizumab and reslizumab

The ERG checked these scenarios against the results obtained by the company model as-is (i.e. without any modifications or corrections).

The first scenario was split into three cases. First, utilities from Willson et al. and Lloyd et al. were used in place of the mapped EQ-5D utilities from the base case (corresponding to the STA for reslizumab). The CS reported an ICER of £32,204 for add-on benralizumab vs. SOC in this case. However, the correct value given by the company's economic model is £32,204.84; therefore the ICER should be rounded to £32,205. Benralizumab dominates both mepolizumab and reslizumab in this scenario, as in the base case. The ERG noted, however, that the total QALYs for both benralizumab and reslizumab should be 14.05 instead of 14.02 (though this does not affect the result).

Second, utilities from Lloyd et al. are used for exacerbations only, and the remaining utilities are kept as in the base case (corresponding to the STA for mepolizumab). The resulting ICERs in the company's model match those in the report. However, the ERG noted that when benralizumab is compared to mepolizumab, total QALYs for benralizumab should be 12.31 (rather than 12.23) and QALYs for mepolizumab should be 12.19 (rather than 12.11). Furthermore, when benralizumab is compared to reslizumab, total QALYs should be 13.30

(rather than 13.24) for both benralizumab and reslizumab. Neither of these errors affect the overall reported ICERs.

Third, raw EQ-5D-5L data were used for all utilities obtained in the SIROCCO and CALIMA trials, rather than the mapped values corresponding to the EQ-5D-3L (the preferred measure in NICE's reference case). The resulting ICERs in the company's model match those in their report.

The second scenario removed the assumption that utilities are treatment dependent. Under this scenario, the ICER for benralizumab vs. SOC is reported in the CS as £38,688. However, the actual value from the economic model is £38,688.96. Therefore, this value should be rounded up to give an ICER of £38,689. The remaining ICERs for this scenario (vs. mepolizumab and vs. reslizumab) in the company's model were consistent with the company report.

The third scenario removed all asthma-related mortality risk from the model, leaving only all-cause mortality from UK National Life Tables. Under this scenario, the ICER for benralizumab vs. SOC is reported in the CS as £67,260. However, the actual value from the economic model is £67,260.86. Therefore, this should be rounded up to give an ICER of £67,261. The remaining ICERs for this scenario (vs. mepolizumab and vs. reslizumab) in the company's model were consistent with the company report.

The fourth scenario removed the consequences of mOCS. The comparison between benralizumab and reslizumab was excluded from these analyses, as the reslizumab NICE population has no baseline mOCS users. This scenario was undertaken in three stages. First, only the additional costs from comorbidities as a result of mOCS use were removed. In this case, the ICER for benralizumab vs. SOC is reported in the CS as £36,983. However, the correct value from the economic model is £34,985. Benralizumab dominates mepolizumab, which is consistent with the CS. Second, only the disutilities arising from mOCS use were removed. The resulting ICERs in the company's model match those in their report. Third, both additional costs and disutilities from mOCS use were removed. Again, the resulting ICERs in the company's model match those in their report.

The fifth and final scenario takes into account the fact that the base case analysis includes the PAS price of benralizumab, but the list prices of mepolizumab and reslizumab, which is extremely likely to overstate the cost-effectiveness of benralizumab. Four errors were found in the ICERs for benralizumab vs. mepolizumab. Three of these were rounding errors; one was a slightly larger discrepancy. These are reported in Table 73. None of these change the results substantively. No errors were found in the ICERs for benralizumab vs. reslizumab.

Table 73 BEN vs. MEPO: errors in scenario analysis ICERs for scenario 5

Mepolizumab PAS discount	ICER reported in CS	ICER from the model, obtained by the ERG
50%	£66,352	£66,326
60%	£112,765	£112,766
70%	£159,205	£159,206
80%	£205,645	£205,646

When varying discounts in 10% increments, the CS found that benralizumab lies above the NICE WTP range of £20,000-30,000 relative to mepolizumab if mepolizumab has a 50% (or better) PAS discount. Benralizumab is dominated by reslizumab if the PAS discount for reslizumab is 60% (or better). The ERG noted that the PAS price of benralizumab represents a [redacted] discount over the list price. If the same level of discount were to be applied to mepolizumab, the resulting ICER for benralizumab vs. mepolizumab would be £46,961, which lies outside the NICE WTP range. However, benralizumab would still dominate reslizumab at this discount level.

5.2.10 Model validation and face validity check

Black box checks and detailed checks on formulae were conducted by the ERG. A detailed list of errors can be found in a separate appendix. Notwithstanding these errors, the model in general was clearly structured, and provided results that closely corresponded to the report (with minor exceptions as stated above, in Section 5.2.2). The errors that were found did not change the ICERs reported in the CS substantially. When all corrections are applied simultaneously, the base case ICER for benralizumab vs. SOC reduced from £34,284 to £34,270.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Derivation of the ERG's base case

The ERG had concerns about the company's choices of parameters and conducted an additional analysis. In Table 74, the impact of the individual components (Items 1 –5) of the ERG's base case on cost-effectiveness, as well as the ERG's base case, composed of all components, are presented together with the company's results. This table was reproduced in Section 1.7.1.

Importantly, AstraZeneca considered SOC as the most important comparator. The ERG, however, believe that *the key comparator* in this appraisal is *mepolizumab* (see Section 1.5 for an explanation).

Table 74 Derivation of PenTAG's base-case ICERs (£ per QALY)

	Item	PenTAG's base case	Company's base case	ICER for BEN+SOC vs		
				SOC	MEPO + SOC	RESLI + SOC
1	Asthma-related mortality	Age-stratified probabilities for hospitalised patients of 65 years of age and older, and for patients of 45-100 years old requiring OCS and NR the probabilities are the same as in the CS; in all other age categories, they were assumed ~2.5 times lower than in the company's model.	See Table 60	£36,398	BEN dominates	BEN dominates
2	mOCS use at baseline	41.7% (Heaney et al., 2010) for all treatments	54.1% for SOC comparison, 78.6% for the MEPO comparison	£36,531	BEN dominates	NA
3	Administration costs of biologics	Costed supervision after the admin of biologics; assumed the same admin time for MEPO and BEN; assumed admin cost for RESLI as in the RESLI appraisal.	Monitoring time not costed; administration of MEPO takes 5 mins longer than for BEN; 55 mins for RESLI	£34,646	BEN dominates	BEN dominates
4	Acquisition cost for RESLI	Based on a bodyweight distribution from Haselkorn et al., (2009) [10] and the vial-based dosing scheme from SmPC for RESLI [9]	75.2kg	NA	NA	BEN dominates
5	Treatment discontinuation rate	0.0041/cycle (average across the pivotal trials)	0.0048/cycle	£34,346	BEN dominates	BEN dominates

Item	PenTAG's base case	Company's base case	ICER for BEN+SOC vs SOC	ICER for BEN+SOC vs MEPO + SOC	ICER for BEN+SOC vs RESLI + SOC
ERG's base case: 1+2+3+4+5			**£39,135**	**BEN dominates**	**BEN dominates**
Company's base case:			**£34,270**	**BEN dominates**	**BEN dominates**

Note: Comparison between benralizumab and reslizumab assumes equal effectiveness (i.e. only costs differ).
NA, not applicable

The detailed results of the base-case pair-wise analyses are presented in the tables below.

Table 75 ERG's base-case results vs. SOC

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**£39,135**
SoC	[redacted]	[redacted]	-	-	**-**

Table 76 ERG's base-case results vs. mepolizumab

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**BEN dominates**
Add-on mepolizumab	[redacted]	[redacted]	-	-	**-**

Table 77 ERG's base-case results vs. reslizumab

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**BEN dominates**
Add-on reslizumab	[redacted]	[redacted]	-	-	**-**

5.3.2 Sensitivity analyses

In this section we present the results of deterministic, probabilistic, and sensitivity analyses for the ERG's base-case.

5.3.2.1 Deterministic sensitivity analyses

Figure 25 Tornado diagram for the ERG's base case vs. SOC

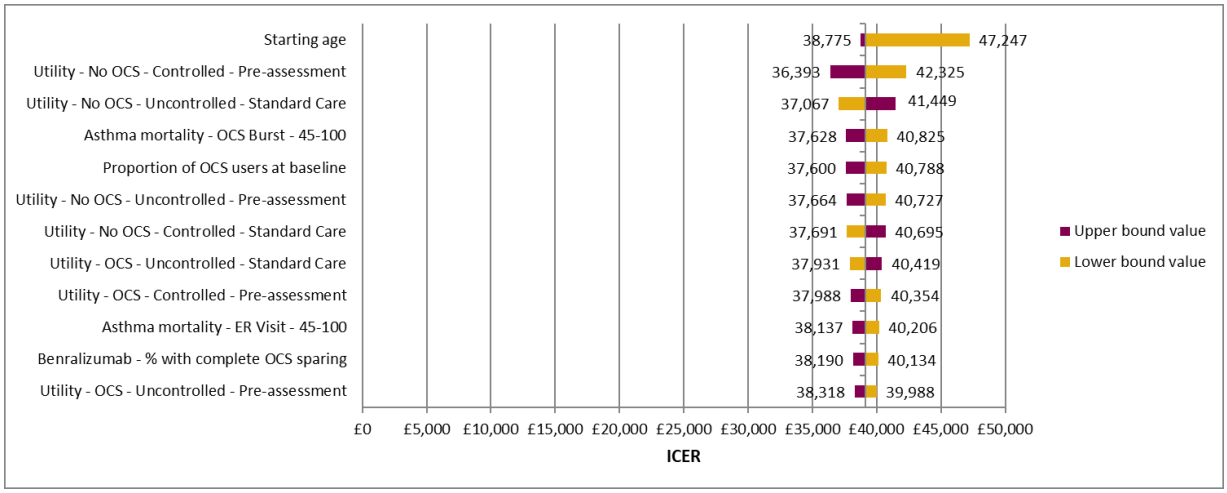
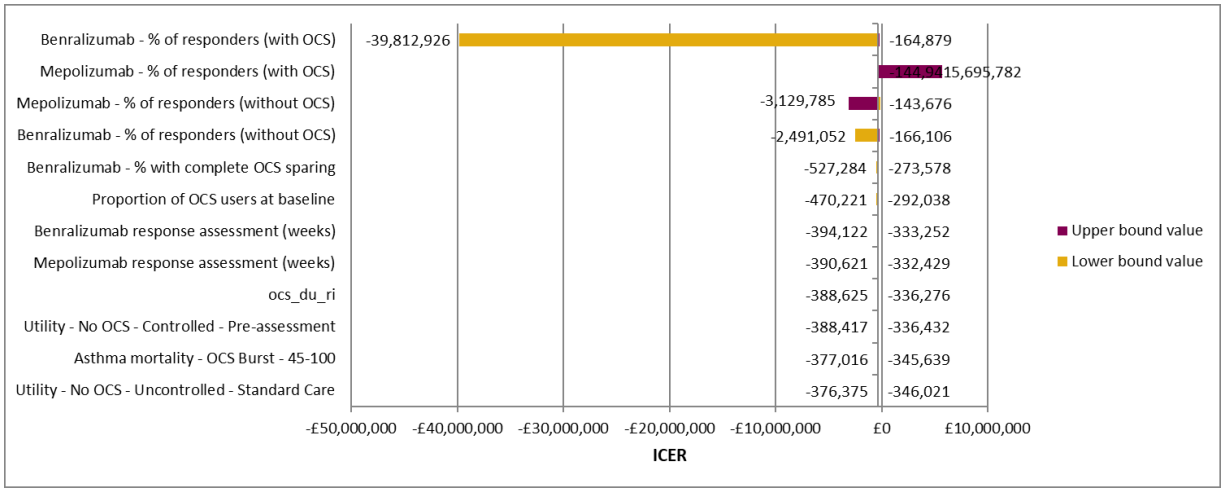


Figure 26 Tornado diagram for the ERG's base case vs. mepolizumab



5.3.2.2 Probabilistic sensitivity analyses

5.3.2.2.1 Benralizumab vs. SOC

Figure 27 ERG's base-case PSA vs. SOC, with £30,000/QALY threshold

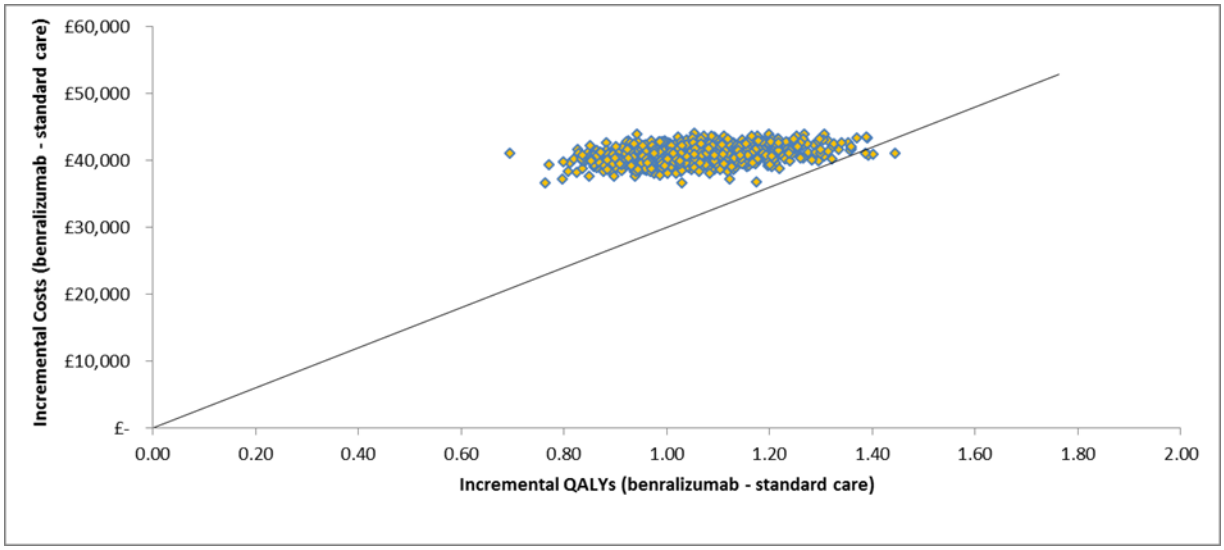
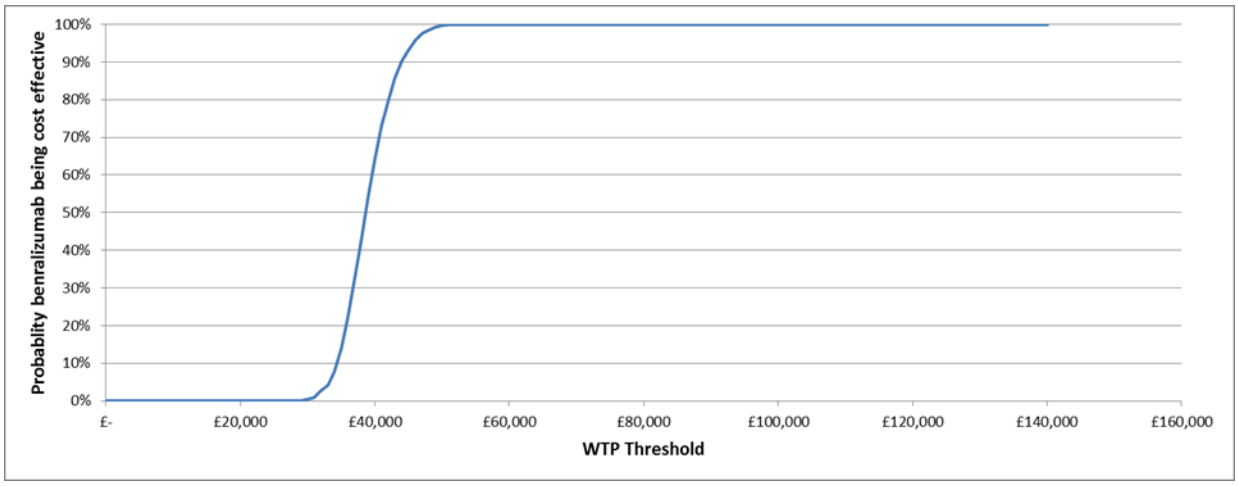


Table 78 ERG's base-case PSA vs. SOC

Technology	Mean total discounted costs (£)	Mean total discounted QALYs	Mean incremental costs (£)	Mean incremental QALYs	Mean ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**£38,562**
SOC	[redacted]	[redacted]	-	-	**-**

Figure 28 CEAC for the ERG's base-case PSA vs. SOC



5.3.2.2.2 Benralizumab vs. mepolizumab

Figure 29 ERG's base-case PSA vs. mepolizumab, with £30,000/QALY threshold

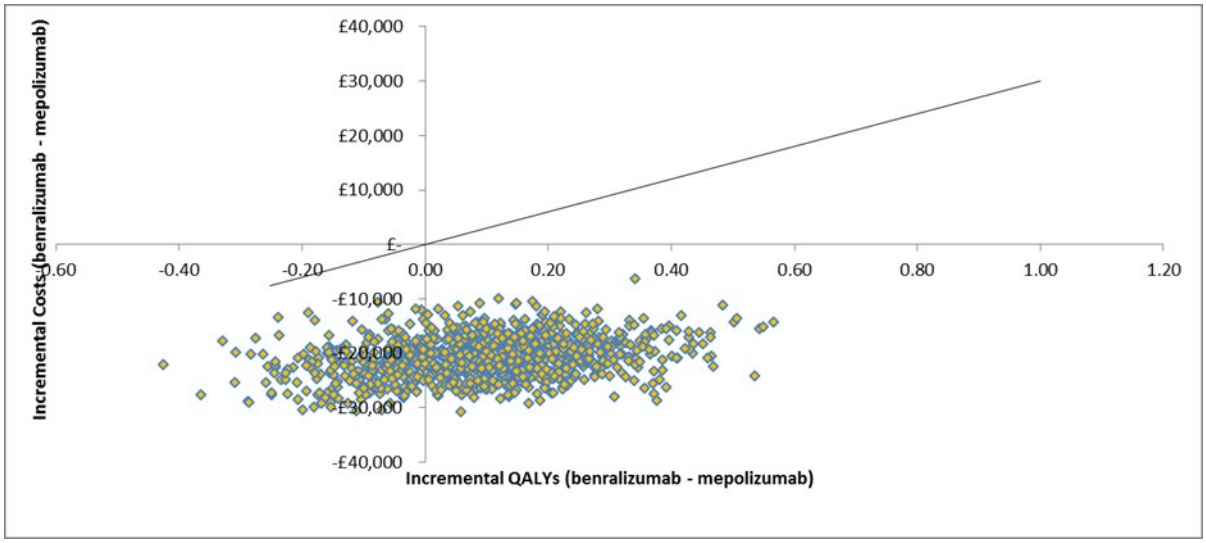
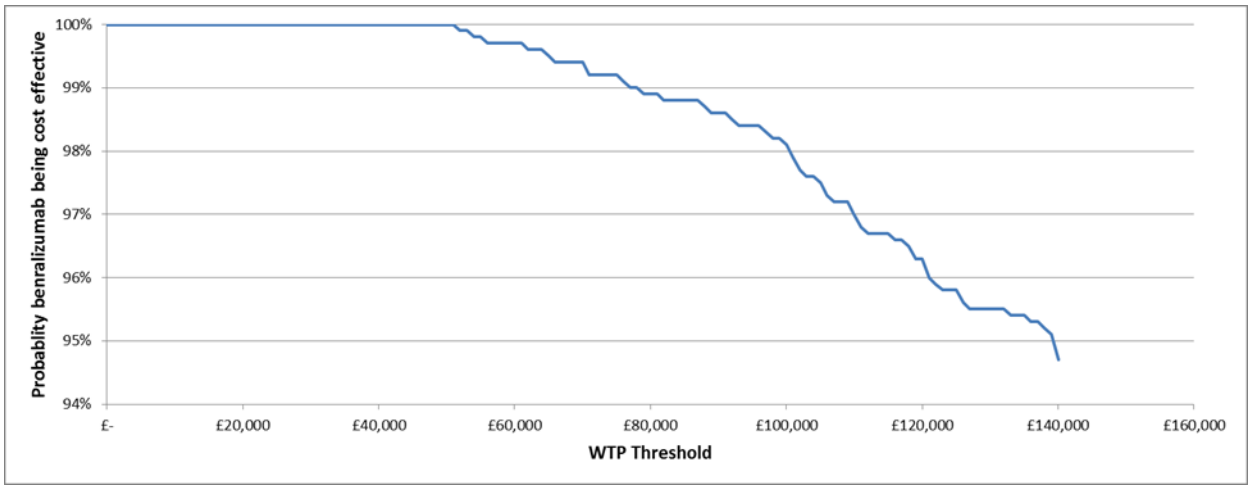


Table 79 ERG's base-case PSA vs. mepolizumab

Technology	Mean total discounted costs (£)	Mean total discounted QALYs	Mean incremental costs (£)	Mean incremental QALYs	Mean ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**BEN dominates**
Add-on mepolizumab	[redacted]	[redacted]	-	-	**-**

Figure 30 CEAC for the ERG's base-case PSA vs. mepolizumab



5.3.2.2.3 Benralizumab vs. reslizumab

Figure 31 ERG's base-case PSA vs. reslizumab, with £30,000/QALY threshold

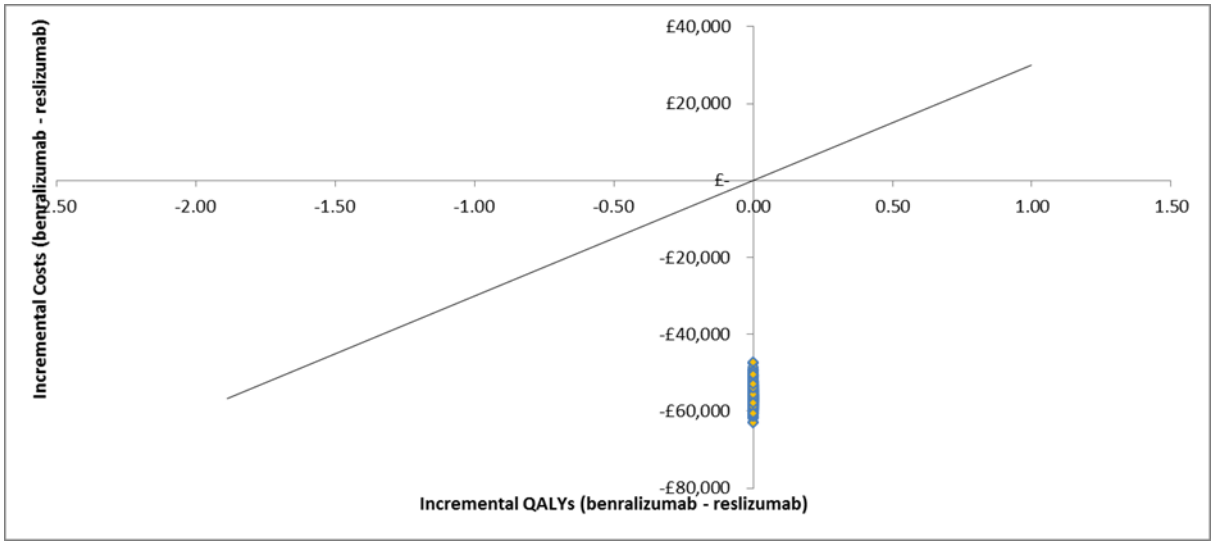
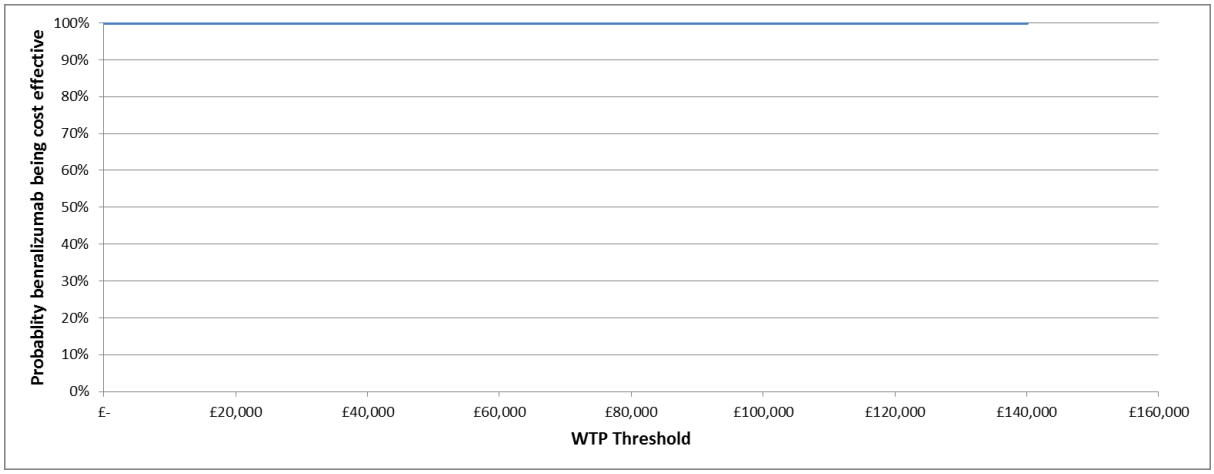


Table 80 ERG's base-case PSA vs. reslizumab (using reslizumab list price)

Technology	Mean total discounted costs (£)	Mean total discounted QALYs	Mean incremental costs (£)	Mean incremental QALYs	Mean ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**BEN dominates**
Add-on reslizumab	[redacted]	[redacted]	-	-	**-**

Figure 32 CEAC for the ERG's base-case PSA vs. reslizumab (reslizumab list price)



5.3.2.3 Scenario analyses

The ERG conducted the following scenario analyses:

- Asthma-related mortality set to zero (Section 5.2.6.5.2)
- mOCS use at baseline of 17% (as in Kerkhof et al. (2017) [6]) (Section 5.2.3.2.4)
- Administration costs of biologics assuming monitoring for the whole duration of treatment, and for the first 16 weeks (Section 5.2.8.3)
- Using EQ-5D-5L health state utility values (Section 5.2.7.1)
- Patient's age at the start of treatment (Section5.2.3.2.2)
- Using the method of calculating acquisition cost of reslizumab as in the CS (Section5.2.8.1.3)
- Using results of a MAIC scenario analysis for exacerbation trials including MUSCA trial (Section 4.4.8)
- Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users (Section 5.2.2.1)

Results are summarised in Table 81 (also reproduced in Section 1.7.2).

Table 81 Scenario analyses relative to the ERG's base case (list prices for comparators)

Assumptions	ICER for BEN vs.		
	SOC	MEPO	RESLI
Set asthma-related mortality to zero	£73,560	BEN dominates	BEN dominates
mOCS use at baseline of 17% (as in Kerkhof et al. 2017) [6]	£44,425	BEN dominates	BEN dominates
Administration costs of biologics assuming monitoring for the entire treatment duration	£40,089	BEN dominates	BEN dominates
Use EQ-5D-5L utilities from the pivotal trials directly, rather than mapped values onto EQ-5D-3L	£40,066	BEN dominates	BEN dominates
Administration costs of biologics assuming monitoring for the first 16 weeks (benralizumab and mepolizumab)	£39,161	BEN dominates	BEN dominates
PenTAG Base Case	**£39,135**	**BEN dominates**	**BEN dominates**
Patient's age at the start of treatment set to 44.9 (as in Heaney et al. (2010) [5])	£38,340	BEN dominates	BEN dominates

Assumptions	ICER for BEN vs.		
	SOC	MEPO	RESLI
Method of calculating acquisition cost of reslizumab as in the CS (RESLI comparison)	NA	NA	BEN dominates
Using results of MAIC scenario analysis for exacerbation trials including MUSCA trial (MEPO comparison)	NA	BEN dominates	NA
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	£38,246	BEN dominates	BEN dominates

Note: Comparison between benralizumab and reslizumab assumes equal effectiveness (i.e. only costs differ).

NA, not applicable

6 End of life

As stated in the CS, the end-of-life criteria are not applicable. The ERG believe that benralizumab would not meet the end-of-life criteria.

References

1. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med. 2007;101(8):1659-64. doi:10.1016/j.rmed.2007.03.006.

2. Roberts NJ, Lewsey JD, Gillies M, Briggs AH, Belozeroff V, Globe DR et al. Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: a retrospective cohort study from 1981 to 2009. Respir Med. 2013;107(8):1172-7. doi:10.1016/j.rmed.2013.04.004.

3. NRAD. Why Asthma Still Kills. The National Review of Asthma Deaths. Available from: https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths2014.

4. Scott S. British Thoracic Society Adult Asthma Audit Report. 2017. https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwi14_Cu1srZAhVEPFAKHVK7CsoQFggpMAA&url=https%3A%2F%2Fwww.brit-thoracic.org.uk%2Fdocument-library%2Faudit-and-quality-improvement%2Faudit-reports%2Fbts-adult-asthma-report-2016%2F&usg=AOvVaw3fFxob9nOrDOLfBIx_6ZWV. Accessed 1 March 2017.

5. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, British Thoracic Society Difficult Asthma N. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65(9):787-94. doi:10.1136/thx.2010.137414.

6. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax. 2017:doi: 10.1136/thoraxjnl-2017-210531. doi:10.1136/thoraxjnl-2017-210531.

7. NICE. Mepolizumab for treating severe refractory eosinophilic asthma. Technology appraisal guidance [TA431]2017.

8. NICE. TA479 - Reslizumab for treating severe eosinophilic asthma. Available from: https://www.nice.org.uk/guidance/ta479. 2017.

9. EMA. Cinqaero (Reslizumab) - Summary of Product Characteristics2017.

10. Haselkorn T, Fish JE, Chipps BE, Miller DP, Chen H, Weiss ST. Effect of weight change on asthma-related health outcomes in patients with severe or difficult-to-treat asthma. Respiratory Medicine. 2009;103(2):274-83.

11. Bleecker ER, FitzGerald, J. Mark, Chanez, Pascal, Papi, Alberto, Weinstein, Steven F. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. The Lancet. 2016;388(10056):2115-27. doi:10.1016/s0140-6736(16)31324-1.

12. FitzGerald JM, Bleecker, Eugene R., Nair, Parameswaran, Korn, Stephanie, Ohta, Ken. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2016;388(10056):2128-41. doi:10.1016/s0140-6736(16)31322-8.

13. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376(25):2448-58. doi:10.1056/NEJMoa1703501.

14. Hernandez Alava M, Wailoo A, Grimm S, Pudney S, Gomes M, Z S et al. EQ-5D-5L versus EQ-5D-3L: The Impact on Cost Effectiveness in the United Kingdom. Value Health. 2018;21(1). doi:10.1016/j.jval.2017.09.004.

15. Ara R, Wailoo A. NICE DSU technical support document 12: the use health utility values in decision models. 2011. http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf. Accessed 1 March 2018.

16. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. Primary care respiratory journal : journal of the General Practice Airways Group. 2007;16(1):22-7.

17. NICE. Guide to the methods of technology appraisal2013.

18. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. The European respiratory journal. 2014;43(2):343-73. doi:10.1183/09031936.00202013.

19. Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S et al. Direct health care costs associated with asthma in British Columbia. Can Respir J. 2010.

20. Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. BMJ. 2009;338.

21. Varricchi G, Senna G, Loffredo S, Bagnasco D, Ferrando M, Canonica GW. Reslizumab and Eosinophilic Asthma: One Step Closer to Precision Medicine? Front Immunol. 2017.

22. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. The Journal of allergy and clinical immunology. 2013;132(5):1086-96.e5. doi:10.1016/j.jaci.2013.05.020.

23. BTS/SIGN. British Guideline on the Management of Asthma. 2016. http://www.sign.ac.uk/pdf/qrg101.pdf. 2017.

24. NHS England. Service specification number 170002/S. Specialised Respiratory Services (adult) – Severe Asthma. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf. 2017.

25. NICE. Asthma: diagnosis, monitoring and chronic asthma management. NICE guideline [NG80]. Available from: https://www.nice.org.uk/guidance/ng80/chapter/Recommendations#principles-of-pharmacological-treatment. 2017.

26. NICE. Omalizumab for treating severe persistent allergic asthma2013 2013. Report No.: Review of technology appraisal guidance 133 and 201.

27. Centre for Reviews and Dissemination UoY. Systematic Reviews. 2009.

28. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2011; 2011.

29. Ferguson GT, FitzGerald JM, Bleecker ER, Laviolette M, Bernstein D, LaForce C et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Respiratory medicine. 2017;5(7):568-76. doi:10.1016/S2213-2600(17)30190-X.

30. Clinicaltrials.gov. Study to Assess Functionality, Reliability, and Performance of a Pre-filled Syringe With Benralizumab Administered at Home. Last updated June 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02417961. 2017.

31. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. The Lancet Respiratory medicine. 2014;2(11):879-90. doi:10.1016/S2213-2600(14)70201-2.

32. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K et al. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. International archives of allergy and immunology. 2016;169(3):135-45. doi:10.1159/000444799.

33. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. Am J Emerg Med. 2015;33(1):14-20. doi:10.1016/j.ajem.2014.09.036.

34. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. The Lancet Respiratory medicine. 2017;6(1):51-64. doi:10.1016/S2213-2600(17)30344-2.

35. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the Quality of Evidence from a Network Meta-Analysis. PLoS ONE. 2014;9(7):e99682. doi:10.1371/journal.pone.0099682.

36. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. NICE_DSU. 2016;December 2016.

37. Haldar P, C. E. Brightling, B. Hargadon, S. Gupta, W. Monteiro, A. Sousa, R. P. Marshall, P. Bradding, R. H. Green, A. J. Wardlaw and I. D. Pavord. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360(10):973-84.

38. Nair P, M. M. Pizzichini, M. Kjarsgaard, M. D. Inman, A. Efthimiadis, E. Pizzichini, F. E. Hargreave and P. M. O'Byrne. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009;360(10):985-93.

39. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. The Lancet Respiratory medicine. 2017;5(5):390-400. doi:10.1016/S2213-2600(17)30125-X.

40. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a

secondary analysis of the DREAM and MENSA studies. The Lancet Respiratory Medicine. 2016;4(7):549-56. doi:https://doi.org/10.1016/S2213-2600(16)30031-5.

41. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-207. doi:10.1056/NEJMoa1403290.

42. Pavord ID, Korn, Stephanie Howarth, Peter Bleecker, Eugene R. Buhl, Roland Keene, Oliver N. Ortega, Hector Chanez, Pascal. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. The Lancet. 2012;380(9842):651-9. doi:10.1016/s0140-6736(12)60988-x.

43. Bel EHW, S. E. Thompson, P. J. Prazma, C. M. Keene, O. N. Yancey, S. W. Ortega, H. G. Pavord, I. D. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97. doi:10.1056/NEJMoa1403291.

44. Schleich FD, S.; Renaud, L. Biomarkers in the Management of Difficult Asthma. Curr Top Med Chem 2016 Apr; 16(14): 1561–1573. 2016.

45. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Tran TN. Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma. The journal of allergy and clinical immunology In practice. 2017;5(4):1050-60 e9. doi:10.1016/j.jaip.2016.12.023.

46. Statistics OoN. National life tables, UK: 2014 to 2016. 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014to2016. Accessed 1 March 2018.

47. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2017. doi:10.1002/hec.3564.

48. Tsuchiya A, Brazier J, McColl E, Parkin D. Deriving preference-based single indices from non-preference based condition-specific instruments: converting AQLQ into EQ5D indices. The University of Sheffield. 2002.

49. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost Effectiveness of Tiotropium in Patients with Asthma Poorly Controlled on Inhaled Glucocorticosteroids and Long-Acting Beta-Agonists. Applied Health Economics and Health Policy. 2014;12(4):447-59. doi:http://dx.doi.org/10.1007/s40258-014-0107-8.

50. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;31(6):800-4. doi:10.1177/0272989X11401031.

51. BNF. British National Formulary. Available from: https://www.bnf.org/. 2017.

52. PSSRU. Unit costs of health and social care. 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/. 2016.

53. Willson J, Mukuria CW, Labeit A, Gunsoy N, Starkie Camejo H, Alfonso-Cristancho R et al. Development of a mapping algorithm between the SGRQ and EQ-5D-5l utility values in a severe asthma population. Value Health. 2016;19 (7):A385.

54. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. Personal Social Services Research Unit, University of Kent, Canterbury. 2017. doi:https://doi.org/10.22024/UniKent/01.02/65559.

Appendix 1. Mortality

The study by Watson et al. was the only study to report mortality risk for acute severe asthma patients hospitalised for asthma. Data were analysed from the CHKS database, specifically admissions with ICD10 codes J45 (asthma, plus sub-codes J45.0, J45.1, J45.8 and J45.9) and J46 (acute severe asthma). Mortality during the admission spell (the period from a live admission to either discharge or death) was then recorded by admission code and stratified by age band (<12, 12–16, 17–44 and ≥45 years) and gender. One of the key limitations with this study is that in the absence of a death certificate the death could not be attributed to asthma with any certainty. However, it was deemed reasonable by Watson et al to assume that asthma was at least a contributory factor in the majority of deaths due to death occurring in the same admission spell, which lasted only a few days in the majority of patients. Time between admission and death was 4 days in acute severe asthma patients. Additionally, no secondary morbidity codes were reported for the patient in over 80% of cases.

The mortality risk reported by Watson et al. is a conditional probability; it represents the probability of death given a hospitalisation for asthma. In order to obtain the asthma-related mortality risk for hospitalised exacerbations in the economic analysis, the mortality risk following hospitalisation was multiplied by the risk of an exacerbation requiring a hospitalisation. Therefore, the age dependent risks are only applied following an exacerbation requiring hospitalisation.

Applying only an asthma related mortality risk to those experiencing an exacerbation requiring a hospitalisation was deemed a conservative approach, as it is known that patients die of asthma exacerbations outside of the hospital setting and benralizumab reduces exacerbations requiring hospitalisation and those requiring an A+E visit or an OCS burst. The NRAD report [3] (identified through hand searching) is the first UK wide investigation into asthma deaths and the largest worldwide study of this kind to date. The study was undertaken over a 3-year period (2011-2014). Extensive information about each death was sought from multiple sources including primary, secondary and tertiary care, as well as ambulance, paramedic and out of hours care providers. Death by location showed that 41% died at home, 23% on the way to hospital and 30% in hospital. Forty-five per cent (87/195) died from asthma without any medical assistance during the final episode; for 65 of these cases, there was no record of them seeking medical assistance, and for 22 cases (11%), there was a record of the patient trying to get help but dying before medical treatment could be provided.

NRAD is considered a valuable source of proxy mortality data for non-hospitalised mortality. It allows an estimation of probability of death for non-hospitalised exacerbation by combining location of death information with probabilities for death for hospitalised exacerbation (Watson 2007).

Asthma deaths from the exacerbation state were therefore calculated using data from [2, 1] and data from the National Review for Asthma Deaths (NRAD) [3].

The approach was optimised to reflect both the mortality attributable to asthma hospitalisation and the inherent variation in this risk across the most granular stratification of age categories available. The approach included the assumption that asthma-related mortality can only occur from the exacerbation state at specific asthma-related mortality rates.

Table 82 Deaths during asthma-related hospital admission (Watson et al.. 2007 [1])

Age band (years)	Deaths during asthma admission	Total asthma admissions	Probability of death during asthma hospital admission [1]
17 – 44	36	9,407	0.00383
45 – 100	177	7,143	0.02478

Source: Table 73, CS

Table 83 Location of asthma-related deaths (NRAD 2014 [3])

Location of death (NRAD)	Number of people	Exacerbation type	Percentage of deaths during exacerbation (NRAD)
Home (private address)	80	OCS burst	46.67%
Nursing/residential home	5		
Holiday	4		
Other	2		
Hospital, pre-hospital arrest	45	ER visit	23.08%
Hospital, arrest in hospital	59	Hospital admission	30.26%

Source: Table 74, CS

Table 84 Percentage of total exacerbations by type

Exacerbation Type	% of total exacerbations seen in pooled SIROCCO/CALIMA
OCS burst	86%
A+E	6.7%
Hospitalised	7.3%

Source: Table 75, CS

The company considered all deaths in Watson as "hospital, arrest in hospital", which accounts for 30% of deaths in the NRAD report, and that the total number of deaths would be 100/30 times greater than those reported in Watson. The additional deaths were regarded as those exacerbations which required an ED visit (23/70) and those required an OCS burst (47/70). The distribution of deaths among hospitalisation, ED visit and OCS burst was assumed constant and independent of the number of deaths reported in hospital.

Therefore, to calculate, for example the probability of death from an exacerbation treated with an OCS burst, the probability of death from a hospitalisation from Watson is adjusted by the percentage of deaths from a hospitalised exacerbation from NRAD and the percentage of exacerbations which were hospitalised in the trial data to give the probability of death from an exacerbation treated with an OCS burst adjusted by the % of deaths from an OCS treated exacerbation from NRAD and the % of exacerbations which were treated with an OCS burst from the trials – as per the formula below

$$\text{Probability of death (OCS burst)} \times \frac{\%\ \text{Exac (OCS burst)}}{\%\ \text{Deaths (OCS burst)}}$$
$$= \text{Probability of death (Hospital admission)} \times \frac{\%\ \text{Exac (Hosp)}}{\%\ \text{Deaths (Hosp)}}$$

Where % Exac (OCS) = Percentage of total exacerbations resulting in OCS burst (from SIROCCO/CALIMA), % Exac (Hosp) = Percentage of total exacerbations resulting in hospital admission (from SIROCCO/CALIMA, % Deaths (OCS) = Percentage of deaths during OCS burst (from NRAD), % Deaths (Hosp) = Percentage of deaths during hospital admission (from NRAD).

So, for example, the probability of death during an exacerbation requiring an OCS burst for patients aged 45-100 equals:

$$\text{Probability of death (Hosp)for patients aged } 45-100$$
$$Watson \times \frac{\%\ \text{Exac (Hosp)}\ \ Trial}{\%\ \text{Deaths (Hosp)}\ NRAD} \times \frac{\%\ \text{Deaths (OCS burst)}\ \ NRAD}{\%\ \text{Exac (OCS burst)}\ \ Trial}$$

With numbers:

$$\text{Probability of death during an OCS burst for patients aged } 45-100$$
$$= 0.00383 \times \frac{0.073}{0.3026} \times \frac{0.4667}{0.860} = 0.000501$$

Table 85 Probability of asthma-related death during OCS burst and ER visit (Watson et al. and NRAD)

Age band (years)	Probability of death during OCS burst (Watson et al. + NRAD)	Probability of death during ER visit (Watson et al. + NRAD)
17 - 44	0.000501	0.003165
45 - 100	0.003240	0.020475

The age band 17-44 is used in the DSA and PSA only.
Source: Table 76, CS

Deriving probabilities of death given an exacerbation treated by a hospitalisation

Review of the literature found that Roberts et al. provided a granular (in terms of age) representation of asthma-related mortality following hospital admission for patients (particularly for patients aged 45 years and over). This study investigated the risk of 30-day case fatality following hospitalisation for asthma in adults in Scotland from 1981 to 2009. The Scottish Morbidity Record Scheme with all asthma hospitalisations for adults (>18 years) with ICD9 493 and ICD10 J45-J46 in the principal diagnostic position at discharge was used. These data were linked to mortality data from the General Register Office for Scotland, with asthma case-fatality defined as death within 30 days of asthma admission (in or out of hospital). Probabilities of death from the study are outlined in Table 86.

Table 86 Probability of death during hospital admission (Roberts et al., 2013)

Number of deaths (from odds ratio in Roberts et al.)	Age band (years)	Number of hospital admissions (Roberts et al.)	Probability of death during hospital admission (Roberts et al.)
89	45 - 54	19,856	0.00448
210	55 - 64	16,474	0.01275
605	65 - 100	21,779	0.02778

Source: Table 77, CS

To best model an ageing population, the relative rate ratios of the probabilities for the age bands, 45 – 55, 55 – 64 and 65 – 100 from Roberts et al. were then applied to the Watson et al. 45 –100 band in Table 85. The adjustment assumed that the total asthma admissions were divided equally between the three age categories in order to provide age-stratified probabilities of death following asthma hospital admission for patients with severe asthma (Table 87). This allows for a more granular measurement of asthma related mortality and represents a more conservative estimation than using Watson alone as it allocates the majority of the mortality risk to the later age groups rather than an average across all. This is also in line with the preferred assumption from the mepolizumab NICE STA [7].

Table 87 Probability of death following hospital admission (Watson 2007, Roberts 2013)

Age band (years)	Probability of death following hospital admission (Roberts et al.)	Relative rate ratio (Roberts et al.)	Assumption that hospital admissions from Watson et al. are divided equally between the age groups	Deaths following asthma admission (Watson et al.) fitted to relative rate ratios (Roberts et al.)	Probability of death following hospital admission (Watson et al. fitted to Roberts et al.)
45 – 54	0.00448	1	2,381	18	0.00756
55 – 64	0.01275	2.82	2,381	51	0.02142
65 – 100	0.02778	6.18	2,381	108	0.04536

Source: Table 78, CS

The asthma-specific mortality rates used in the model summarised in In previous economic evaluations relevant to this appraisal (i.e. of mepolizumab, reslizumab, and omalizumab) asthma-related mortality was identified as one of the key drivers of the cost-effectiveness of the treatments.

No deaths due to asthma were observed in the pivotal trials. Therefore, probabilities of asthma-related mortality were estimated from alternative published sources. The company conducted a literature review of asthma-related mortality to identify UK studies reporting mortality rates as a result of severe asthma, or risk factors for asthma-related death. The company noted that data on mortality from Watson 2007, Roberts 2013 and the NRAD report [3] were used in the base-case analysis. However, no further details related to the literature review was provided in the CS.

In the model, the company assumed that a patient could die from asthma only after a clinically significant exacerbation. For exacerbations requiring a hospital admission, the model uses mortality data from Watson et al. (2007) combined with Roberts et al. (2013) and for exacerbations not requiring a hospital admission (i.e. OCS burst and ER visits) from Watson et al. (2007) combined with locations from the National Review for Asthma Deaths (NRAD) [2, 1, 3]. This approach was consistent with the method used in the mepolizumab NICE STA (TA431) [7].

Deriving probabilities of death given an exacerbation treated by an OCS burst or an A+E visit

Watson et al. reported mortality incidence, stratified by age, within an acute severe asthma population following a hospital admission in 2000-2005. However, this does not provide estimates for the probability of death for an exacerbation treated with either an OCS burst or an A+E visit. Therefore, for exacerbations not requiring a hospital admission (i.e. OCS burst and A+E visits) the data were combined with the results from the NRAD and the percentage of each type of exacerbation from the SIROCCO/CALIMA trials as outlined in Table 60 and Appendix 1. The NRAD report only provides the percentage of deaths which occur from each type of exacerbation, however, the trial data shows that certain types of exacerbation are more frequent than others. A detailed account on how the probabilities of asthma-related death were derived is presented in Appendix 1.

Table 60 were applied to the population in the exacerbation states each cycle in proportion to each type of exacerbation Table 84 Percentage of total exacerbations by type.

Appendix 2. SOC costs

Table 88 Calculation of weighted average ICS/LABA costs

ICS/LABA	Cost per inhaler	Unit	Strength	Dose/day	Cost/ Cycle	Mkt Share
Fostair	£29.32	120	200/6	4	£13.72	25.1%
Flutiform	£45.56	120	10/250	4	£21.32	5.9%
Symbicort	£28	60	400/12	4	£26.21	28.3%
Duoresp	£29.97	60	320/9	4	£28.05	7.2%
Seretide Accuhaler	£40.92	60	50/500	2	£19.15	11.4%
Seretide Evohaler	£59.48	120	25/250	4	£27.83	9.5%
Relvar	£29.50	30	22/184	1	£13.80	5.7%
AirFluSal	£39.95	120	25/250	4	£18.69	0
Sirdupla	£44.61	120	25/250	4	£20.88	7.0%
Sereflo	£39.95	120	25/250	4	£18.69	0
Weighted Average					**£21.21**	

Appendix 3. Health state costs

Table 89 Unit costs and medical resource use by health states (weekly) [53] [53, 49]

Resource	Unit Cost (AstraZeneca)	Health state		
		Controlled Asthma	Uncontrolled Asthma	Exacerbation
Outpatient Visits	**Cost per Visit**	**N visits per patient/week**		
Visit to GP	£36 (PSSRU)	0.035	0.14	1.31
Visit to Nurse	£11.10 (PSSRU)	0.059	0.16	0.94
Visit to Specialist	£160.32	0.0243	0.094	0.44
Home Visits	Cost per Visit	N visits per patient/week		
Visit from GP	£82.68 (PSSRU)	0.00507	0.025	0.21
Visit from Nurse	£19.70 (PSSRU)	0	0	0.0034
Lab Tests/Procedures	Cost per test/procedure	N procedures per patient/week		
Spirometry	£28.20 (Willson 2014)	0.027	0.049	0.30
Flu Vaccine	£6.32 (Willson 2014)	0.020	0.020	0
Desensitisation	£175.32 (Willson 2014)	0.00612	0.0087	0
Inpatient Resource used	Cost per episode	N events per patient/week		
Asthma exacerbation related hospitalisation	£2,692 (NHS Ref Costs, weighted average of DZ15M/N/P)	0	0	0.028
A+E visit only	£137.74 (NHS Ref Costs, Weighted average of Emergency Medicine codes)	0	0	0.054
A+E visit + Hospitalisation	£2,829.74 (NHS Ref Costs)	0	0	0.03

Resource	Unit Cost (AstraZeneca)	Health state		
		Controlled Asthma	Uncontrolled Asthma	Exacerbation
Ambulance + hospitalisation	£2,788.25 (NHS Ref Costs, Weighted average of ambulance codes)	0	0	0.0016
Ambulance + A&E + Hospitalisation	£2,925.99 (NHS Ref costs)	0	0	0.003
Hospitalisation including ICU stay	£3,686.45 (NHS Ref costs, DZ15M/N/P + XC06Z (ICU stay))	0	0	0.009

p564 (committee papers for reslizumab appraisal dated 15 November, 2016) [8]

Table 90 Health states and associated costs in the economic model per cycle

Health State	Item	Treatment Arm							
		Benralizumab		SOC		Mepolizumab		Reslizumab	
		Value	Reference	Value	Reference	Value	Reference	Value	Reference
Controlled Asthma	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption	£0		£9	NICE TA431 PSSRU	£49.5	NICE TA479[8] PSSRU
	SOC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF
	Health State	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU	£16.38	Willson, PSSRU
	Total	Year 1: £[redacted]		£37.59		£466.59		£649.57	

Health State	Item	Treatment Arm							
		Benralizumab		SOC		Mepolizumab		Reslizumab	
		Value	Reference	Value	Reference	Value	Reference	Value	Reference
		Subsequent Years: £[redacted]							
Uncontrolled Asthma	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption	£0		£9	NICE TA431 PSSRU	£49.5	NICE TA479[8] PSSRU
	SOC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF
	Health State	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU	£53.97	Willson, PSSRU
	Total	Year 1: £[redacted] Subsequent Years: £[redacted]		£75.18		£504.18		£687.16	
Exacerbation	Treatment	Year 1: £[redacted] Subsequent Years: £[redacted]	AstraZeneca	£21.21	BNF	£420	BNF	£562.48	BNF, Reslizumab SPC
	Administration	£4.50	Assumption PSSRU	£0		£9	NICE TA431 PSSRU	£49.5	NICE TA479[8] PSSRU
	SOC	£21.21	BNF	N/A		£21.21	BNF	£21.21	BNF

Health State	Item	Treatment Arm							
		Benralizumab		SOC		Mepolizumab		Reslizumab	
		Value	Reference	Value	Reference	Value	Reference	Value	Reference
	Health State	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU	£736.29 (£184.07 adjusted to cycle length)	Willson, PSSRU
	Total	Year 1: £[redacted] Subsequent Years: £[redacted]		£205.28		£634.28		£817.26	

Appendix 4. Transition probabilities used in the model

Table 91 Transition probabilities – SOC (non mOCS), Base Case Population, All Weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 92 Transition probabilities – Benralizumab (non mOCS), Base Case Population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 93 Transition probabilities – Benralizumab responder (non mOCS), Base Case Population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 94 Transition probabilities – SOC (mOCS), Base Case Population, All Weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 95 Transition probabilities – Benralizumab (mOCS), Base Case Population, 0-52 weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 96 Transition probabilities – Benralizumab responder (mOCS), Base Case Population, >52 weeks

		Visit i+1

		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	**Controlled**	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 97 Transition probabilities – Benralizumab (non mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 98 Transition probabilities – Mepolizumab (non mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 99 Transition probabilities – Benralizumab responder (non mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 100 Transition probabilities – Mepolizumab responder (non mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 101 Transition probabilities – SOC (non mOCS), Mepolizumab NICE recommended population, All Weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 102 Transition probabilities – Benralizumab (mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 103 Transition probabilities – Mepolizumab (mOCS), Mepolizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 104 Transition probabilities – Benralizumab responder (mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 105 Transition probabilities – Mepolizumab responder (mOCS), Mepolizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Transition probabilities calculated using RRs from the MAIC in the full trial populations for benralizumab and mepolizumab, applied to the mepolizumab NICE recommended population. Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 106 Transition probabilities – SOC (mOCS), Mepolizumab NICE recommended population, All weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 107 Transition probabilities – Benralizumab (non mOCS), reslizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]

	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 108 Transition probabilities – Reslizumab (non mOCS), reslizumab NICE recommended population, 0-52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 109 Transition probabilities – Benralizumab responder (non mOCS), reslizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 110 Transition probabilities – Reslizumab responder (non mOCS), reslizumab NICE recommended population, >52 weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)

Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 111 Transition probabilities – SOC (non mOCS), Reslizumab NICE recommended population, All weeks

		Visit i+1			
		Controlled	Uncontrolled	Exacerbation (Controlled)	Exacerbation (Uncontrolled)
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Appendix 5. Sensitivity analyses undertaken under company assumptions

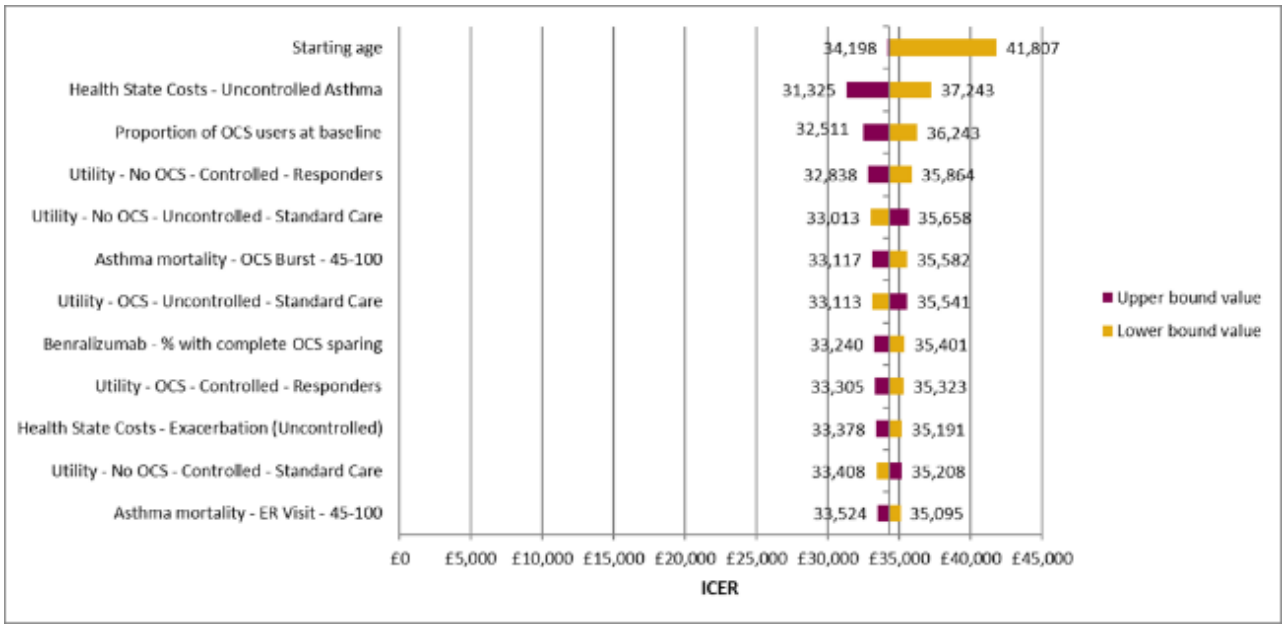


Figure 33 DSA vs. SOC from company

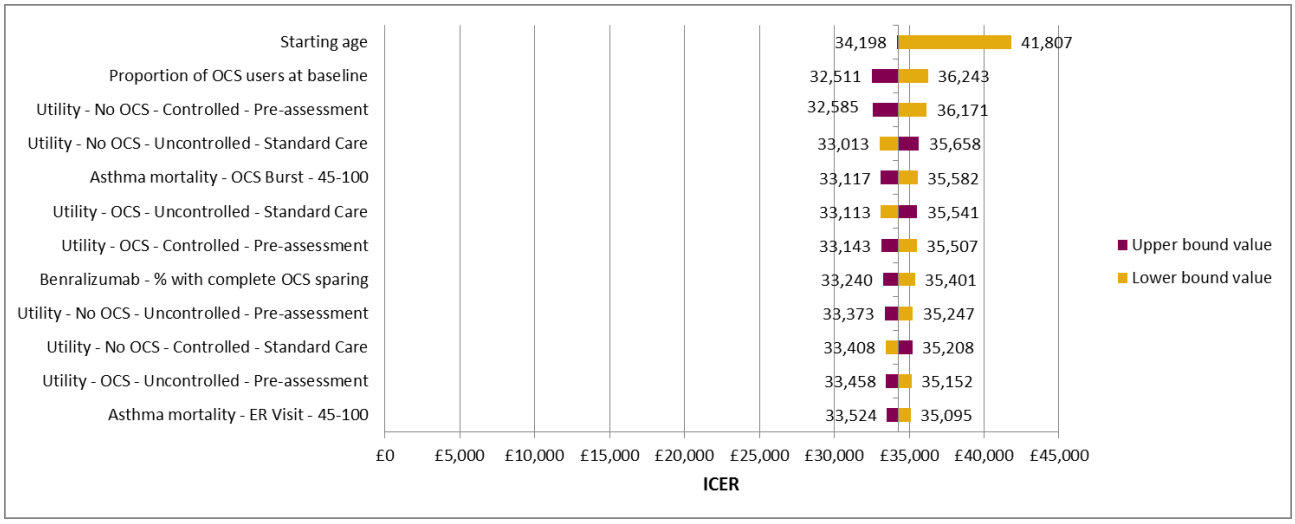


Figure 34 DSA vs. SOC run by the ERG (with corrected 20% limits)

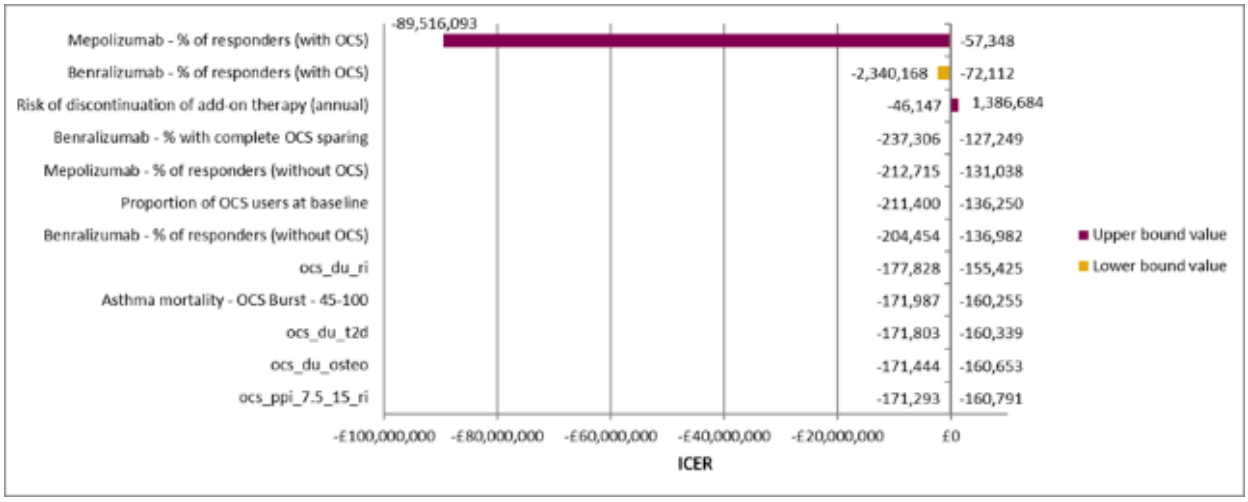


Figure 35 DSA vs. mepolizumab from company

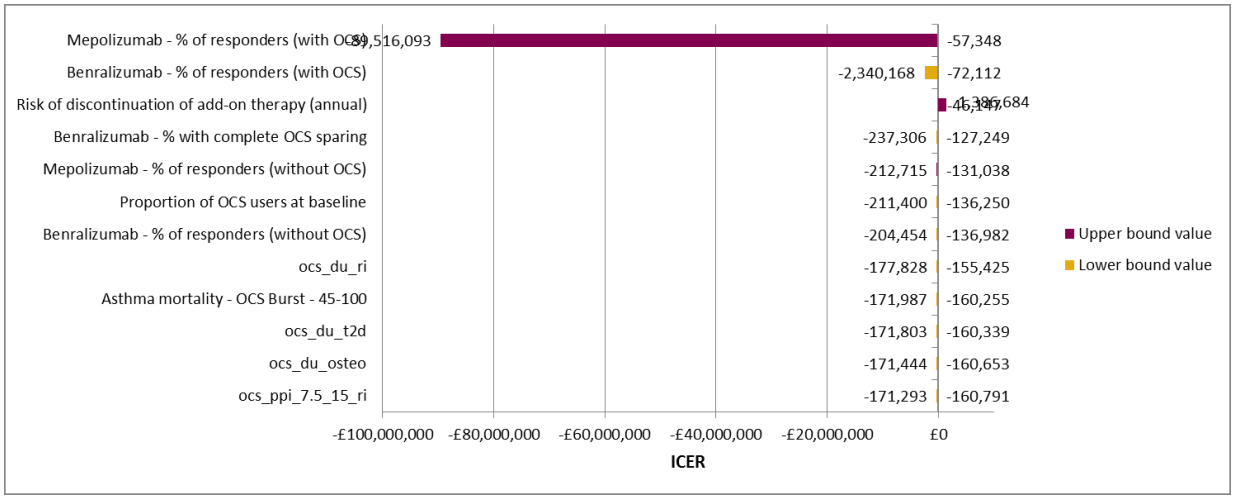


Figure 36 DSA vs. mepolizumab run by the ERG (with corrected 20% limits)

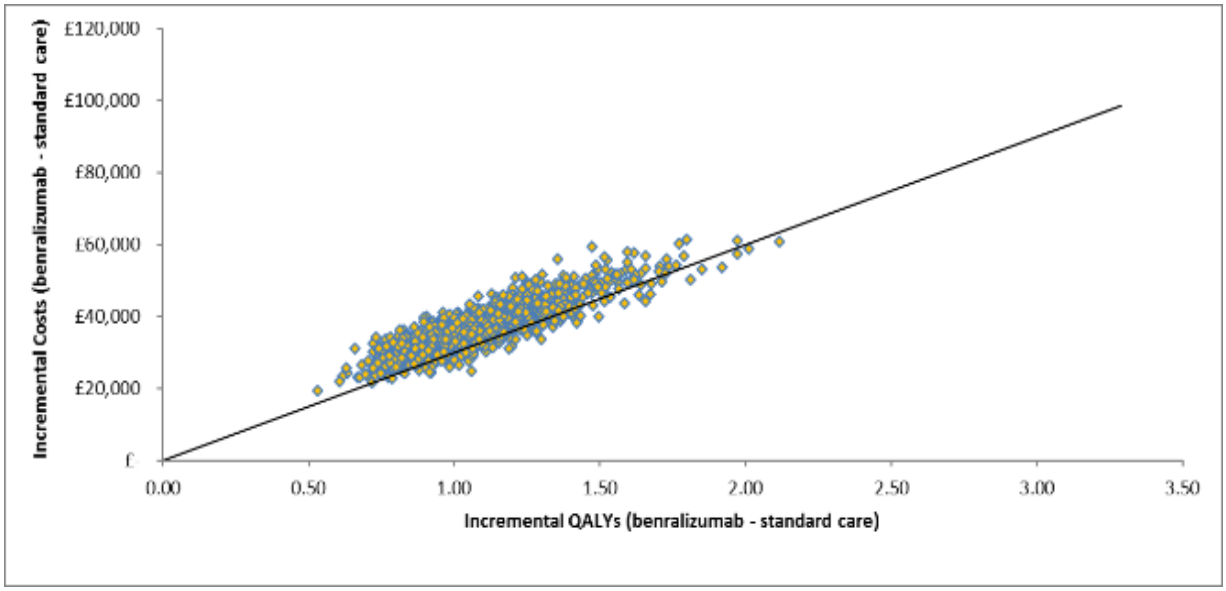


Figure 37 PSA vs. SOC from company

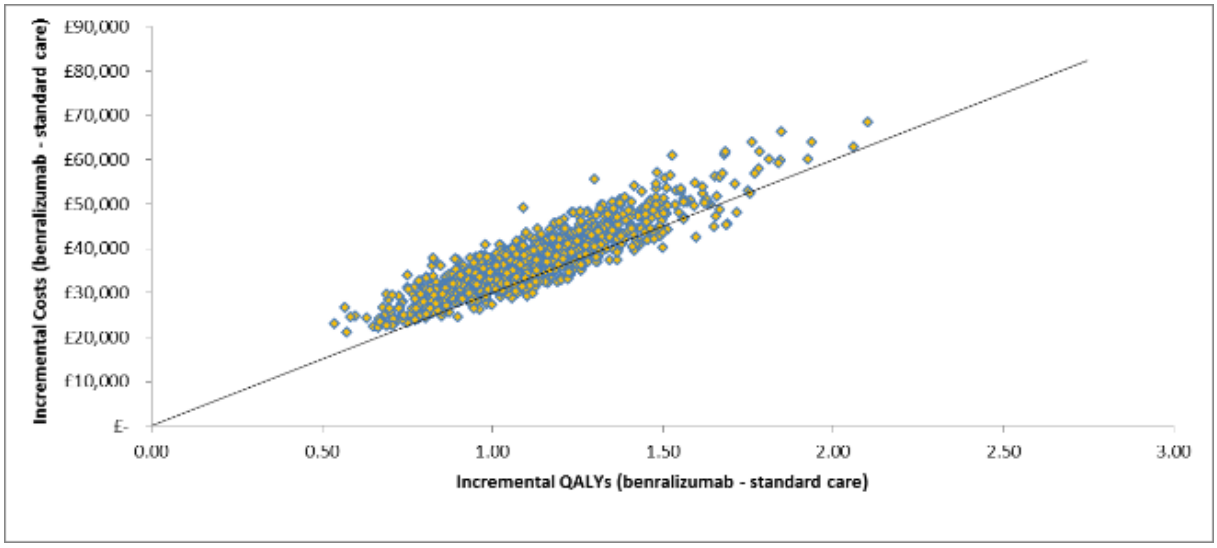


Figure 38 PSA vs. SOC run by the ERG

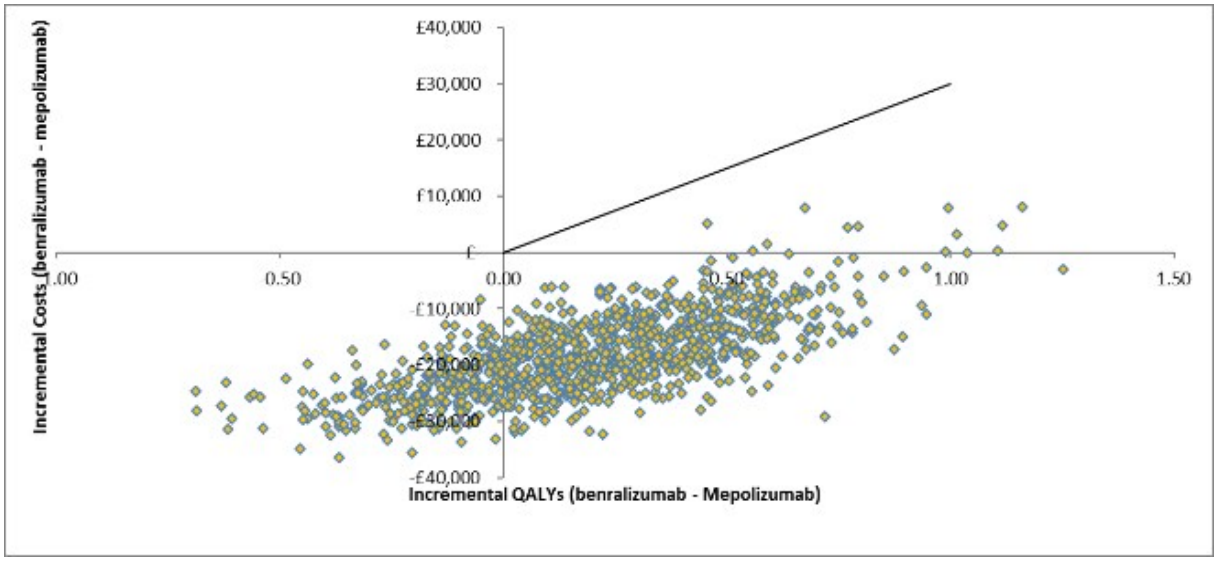


Figure 39 PSA vs. mepolizumab from company

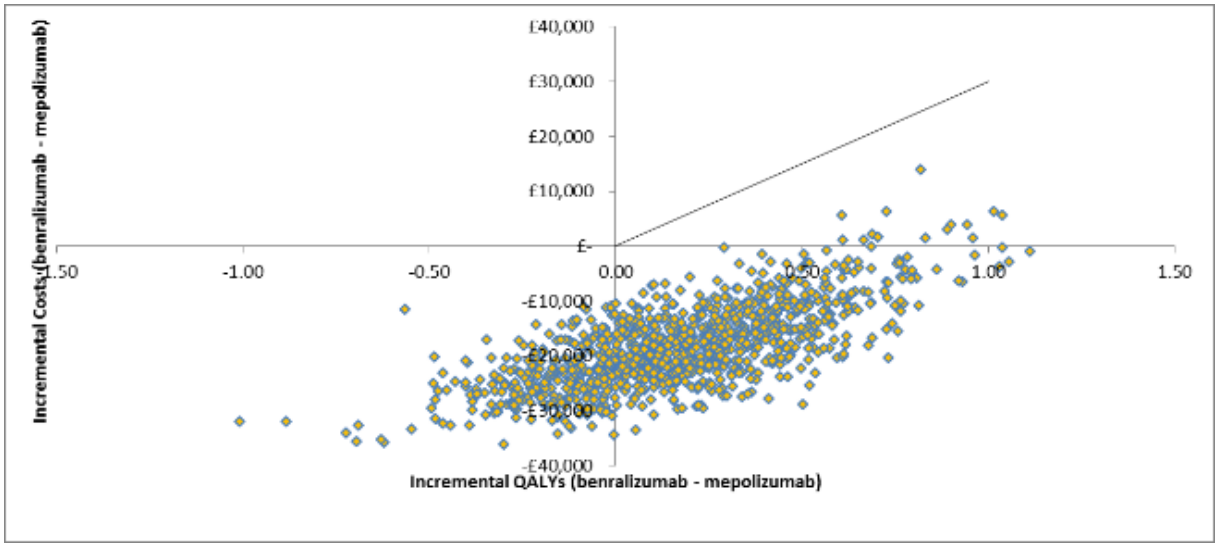


Figure 40 PSA vs. mepolizumab run by the ERG

Appendix 6. Additional clinical effectiveness data

[redacted]

[redacted]

[redacted]

115 [redacted]

[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Benralizumab for treating severe eosinophilic asthma [ID1129]

You are asked to check the ERG report from PenTAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 21 March 2018** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Key Points

We would like to highlight three key points described in the ERG report, where we consider there is strong justification for amendments:

1. **Percentage of patients with maintenance OCS in the model:** The ERG have reduced the percentage of patients with maintenance OCS in the model from 54.1% (SOC comparison); and 78.6% (mepolizumab comparison) to 41.7%, for both comparisons versus SOC and mepolizumab. The ERG have used a data source for the 41.7%, which includes severe asthma patients; and is not specific to the population where a recommendation is sought (patients with 300+ EOS; and 3+ exacerbations in the prior year OR receiving maintenance OCS). Therefore, the 41.7% may be an underestimate. The figures in the manufacturer submission (54.1%; and 78.6%) are from robust UK RWE in the population where a recommendation is sought; and should be used within the economic model.
2. **Asthma-related mortality:** The ERG have used a data source (BTS 2016 audit) including a general asthma population; and limited to two months of data, which may underestimate mortality in the severe asthma population relevant to this appraisal; and may be affected by the seasonal nature of asthma due to the short data collection period. The key data source used in the manufacturer submission (Watson et al, 2007) is in severe asthma patients, a population relevant to the decision problem; and with a considerably longer data collection period of 5-years; and should therefore be used to inform the model.
3. **Benralizumab efficacy results by geographical region:** The ERG noted that *"the treatment effect of benralizumab appeared to consistently favour benralizumab in both trials only for the Asian population".* We would like to reiterate that neither SIROCCO nor CALIMA were powered to detect differences in exacerbation rates by geographical region. Correspondingly, the confidence intervals for the European populations are wide, with the upper bound crossing 1 in CALIMA. Nevertheless, the hazard ratio point estimates for the European populations are comparable to (and numerically better than) those of the overall population. We therefore ask that this statement is removed or clarified.

Please see below for further information on each of these points.

Issue 1 Percentage of patients using maintenance OCS (mOCS) in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Pages 150, 152 and 187 The ERG state that "all comparisons should have been made assuming the same proportion of mOCS users at baseline" and that this percentage should be 41.7% as reported in Heaney et al (2010)	We believe that the data used to calculate the percentage of patients using mOCS at baseline in the ERG model is not representative of the specific population for which a recommendation is sought; and therefore this number should be reverted to those in the original company submission (54.1% for the SOC comparison; and 78.6% for the mepolizumab comparison).	**The percentage of patients using mOCS at baseline must be calculated for the population in question; and specific for the comparisons vs SOC and mepolizumab - therefore the ERG's preferred figure may underestimate this value.** Our calculation of the percentage of patients using mOCS at baseline is calculated based on the population for which we seek a recommendation for benralizumab i.e. those patients with a blood eosinophil count ≥300 cells per µl AND either ≥3 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months OR treatment with continuous OCS over the previous 6 months.. Within this population there are 2 distinct sub-populations, patients who have ≥300 eosinophils and ≥3 exacerbations in the prior year (population 1), and patients who are using mOCS and have ≥300 eosinophils (population 2). In order to reflect UK clinical practice, the percentage of patients using mOCS at baseline must reflect the relative sizes of populations 1 and 2. The ERGs source of the percentage of patients using mOCS at baseline is based on a cross-sectional registry study, which includes all severe asthmatics regardless of eosinophil count or exacerbation history, this will effectively have the effect of inflating population 1, and therefore reducing the relative size of population 2. Further to this in regards to the statement that "all comparisons should have been made assuming the same proportion of mOCS users at baseline", given the above it follows that should population 1 be restricted from patients who have ≥300 eosinophils and ≥3 exacerbations in the prior year to patients who have ≥300 eosinophils and ≥4	The ERG agree that the percentage of patients on mOCS at baseline should reflect that in the population under consideration. Since this assumption is the key driver of the ICERs for the comparisons versus SOC and MEPO, we requested the pooled SIROCCO/CALIMA dataset, but it was not provided by AstraZeneca. The ERG noted (p. 164, company's submission): "In order to calculate the percentage of patients in each population who would be dependent on mOCS at baseline in UK clinical practice, an analysis of the Kerkhof 2017 paper, a UK observational research study, was undertaken. For a full description of the baseline characteristics refer to Table 22". However, the proportions reported by Kerkhof - 16.5% in patients 18-64 y.o. and 17.1% in patients >=65 y.o. (Table 54, p. 150, ERG's report) - were substantially lower than those in the company's base case. Also, as shown in Table 22 (company's submission) which the company referred to, *only about 23% of patients in pooled SIROCCO/CALIMA* dataset were on mOCS at baseline. We agree that there might be a difference in mOCS use at baseline in the base-case and MEPO populations. However, we believe that the estimate of 41.7% reported by Heaney et al. (2010) is more representative of the UK clinical practice than the company's assumption of 54.1% for the SOC comparison, and 78.6% for the mepolizumab

		exacerbations in the prior year (i.e. the population within which mepolizumab is recommended), then the relative size of population 2 (which is unchanged) would be greater and thus require comparisons to be made using a different proportion of mOCS users at baseline.	comparison. **Action:** The statement that **"**all comparisons should have been made assuming the same proportion of mOCS users at baseline" has been removed from the ERG's report.

Issue 2 Asthma related mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 163 to 166 The ERG notes that a more recent publication from the BTS 2016 audit (including a general asthma population) shows a lower probability of death per hospital admission than the data used in the company economic model and thus reduces all mortality probabilities in the model by a factor of 2.5.	We believe that the data used to modify the mortality rates in the ERG model is not representative of the decision problem and population in question in this appraisal and therefore the mortality rates should be reverted to those in the original company submission, which are based on a severe asthma	**The mortality rates used in the company submission is more relevant to the severe asthma population in this appraisal and therefore the ERG's preferred rates may underestimate asthma mortality** The data presented by the ERG to justify their adjustments is based on an audit of hospital admissions for adult patients with asthma during the period of 1 September to 31 October 2016. We feel that this data is less relevant to this decision problem than the probability data from Watson et al, 2007 for the following reasons: The data is captured from all hospitalised patients regardless of disease severity, we have sought external clinical expertise in this matter which confirms that patients with severe asthma are at a higher risk of death from an exacerbation compared to the asthma population as a whole. "Severe asthmatics often have worse lung function and are already on fairly maximal therapy. Therefore when they become poorly-controlled there is less of a window on which to act and fewer additional treatments to add in to avoid a bad outcome" - anonymous clinical opinion. This is further demonstrated within the Watson paper itself, where the probabilities of death following admission are lower for Asthma (J45) than they are for Acute Severe Asthma (J46) (• **Table 1** and **Table 2** below). The data used from Watson which	The ERG agree that seasonality is an important factor for asthma which might not have been captured in the BTS 2016 audit. However, the major reasons for using the reduced mortality rates in the ERG's base case were the trend data reported in NRAD (Fig 23, ERG's report) clearly showing *a significant reduction in asthma death during the last several decades*, and the fact that some of the evidence sources used by the company did not reflect *the recent* clinical practice. Also, in the NRAD report which was used by AstraZeneca to parameterise asthma mortality risk, it is stated that the majority of people (57%) who died from asthma between February 2012 and January 2013, "were not recorded as being under specialist supervision during 12 months prior to death". However, the patient population considered in this appraisal are those

	population.		underpins all probability calculations in the company model is specific to patients with severe asthma and therefore the more relevant source to use for this appraisal • The data is captured over a 2-month period. As asthma is a variable disease and there is a significant amount of seasonality within the prognosis, it is unlikely that this 2-month period captures the full extent of the risk of death associated to an asthma exacerbation. In contrast, the Watson paper covers a 5 year period from 2000 to 2005. • The approach and data sources used in the company model also follows the precedence set in the appraisal for mepolizumab in severe eosinophilic asthma.	patients *who have been on asthma treatment during the previous 12 months*. Our clinical expert, Prof Halpin, confirmed that deaths due to asthma *in people who are concordant with appropriate therapy* are relatively uncommon. We therefore believe that the mortality in the patient population relevant to this appraisal should be lower than the company's estimates derived from the NRAD report. **No action required**

Table 1: Deaths during asthma-related hospital admission for Asthma (Watson et al. 2007)

	Age band (years)	Deaths during asthma admission	Total asthma admissions	Probability of death during asthma hospital admission (Watson et al. 2007)
Asthma (J45)	**17 – 44**	32	62,102	0.000515281
Asthma (J45)	**45 – 100**	798	67,060	0.011899791

Table 2: Deaths during asthma-related hospital admission for acute severe asthma (Watson et al. 2007)

	Age band (years)	Deaths during asthma admission	Total asthma admissions	Probability of death during asthma hospital admission (Watson et al. 2007)
Acute Severe Asthma (J46)	**17 – 44**	36	9,407	0.003826937

Acute Severe Asthma (J46)	**45 – 100**	177	7,146	0.024769102

Issue 3 Regional differences in efficacy, ERG report, pages 20, 79, 137

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
"The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both trials only for the Asian population" We would like to reiterate that neither SIROCCO nor CALIMA were powered to detect differences in exacerbation rates by geographical region. Correspondingly, the confidence intervals for the European populations are wide, with the upper bound crossing 1 in CALIMA. Nevertheless, the hazard ratio point estimates for the European populations are comparable to (and numerically better than) those of the overall populations: • In SIROCCO, the exacerbation rate reduction was 0.49 (0.37, 0.64) in the overall population versus 0.30 (0.17, 0.52) in the European population • In CALIMA, the exacerbation rate reduction was 0.72 (0.54, 0.95) in the overall population versus 0.64 (0.32, 1.28) in the European population	The ERG's statement should be removed or reworded to reflect the explanation presented in column 1	We feel that the ERG's statement could be misleading about the efficacy of benralizumab in a European population as it currently stands	AstraZeneca did not provide a pooled analysis (CALIMA and SIROCCO) of the efficacy for the regions. This would have provided fairer estimates for individual regions than reported in individual trials. **No action required**

Issue 4 Selective reporting, ERG report, pages 21, 31, 54, 56, 58,110, 136, 138

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
"There was evidence of selective outcome reporting, whereby outcomes [redacted] All measured outcomes were reported in the CSRs, which were provided to the ERG. We reported primary and key secondary outcomes, as well as secondary outcomes relevant to the model in the company submission; in the interests of conciseness and clarity, we did not seek to reproduce every secondary outcome from the CSRs. Further, the endpoints reported in our submission included those found to be most	We believe that the statement around selective reporting should be corrected, including in Tables 7, 8 & 9 on pages 54,56, & 58	Selective reporting did not occur.	Outcome reporting bias – the selection for publication of a subset of the original recorded outcome variables on the basis of the results – is an under-recognised problem that can affect conclusions of

important to respiratory specialists in recent market research (reduced exacerbation frequency/severity; reduced steroid burden; QoL), and/or those reported in the mepolizumab and reslizumab submissions (i.e., past precedence). In terms of outcomes considered in the MAIC and model inputs, we selected these according to the primary and key secondary endpoints of benralizumab trials that were also reported in the mepolizumab and reslizumab trials, i.e., endpoints enabling a comparison were included in the MAIC, and informed the clinical inputs of the model.	(in the ERG judgement column for the relevant question)		systematic reviews. The ERG noted that in all three key trials the company had measured all the secondary outcomes they pre-defined in their protocols (with all data reported in unpublished CSR), but failed to report all their results in published journal articles. The ERG recognise that this outcome reporting bias was limited only to secondary outcome measures in all three pivotal trials and acknowledge that outcome reporting bias is common in many RCTs that collect a large number of secondary outcome measures. However, the ERG maintains that outcome reporting bias has occurred and that this is an issue worthy of note in the report. **No action required**

Issue 5 Percentage of patients who respond to mepolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 146: The ERG notes in their report that "Of note, in the MEPO appraisal, the percentage of patients meeting continuation criteria was 97.1% for MEPO (based on MENSA trial), which is substantially higher than the proportion assumed in the company's model"	We ask that this statement is removed as it is based on a historical definition of response which is not the one included in the final mepolizumab recommendation.	**The percentage of patients responding to mepolizumab quoted in the ERG report is based on an outdated definition of response (from GSK manufacturer submission), which has been superseded by the TAG response definition. The benralizumab company submission uses the final mepolizumab TAG responder criteria.** The number of 97.1%, while correct from the company submission for mepolizumab is based on a continuation criterion of patients exacerbation rates not increasing. The final guidance for mepolizumab states that patients should "continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control." This is the continuation criteria used within the company model and the [redacted] of patients who respond to mepolizumab is reflective of this.	It was not clear from the company's submission how the estimate of [redacted] was derived but this has been clarified here. **Action:** The report has been updated to reflect this. The statement on p. 146 has been removed as suggested.

Issue 6 Rate of Hospitalisations

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 156 to 159. The ERG notes the RR of the various types of exacerbation in the SIROCCO/CALIMA trials, and states "the company's model predicted twice higher rate of hospitalisation in SOC patients; underestimated the rate of exacerbations requiring ER visit, and overestimated OCS rate in BEN patients"	We believe this section is misleading as it does not take into account the entirety of the evidence and therefore should be removed	**The data comparison presented in this section does not take into account the entirety of the evidence (ZONDA and the responder analysis) and therefore is misleading.** The trial evidence quoted by the ERG is solely from the pooled SIROCCO/CALIMA trials and the model data quoted is extrapolated over the entire time horizon. We believe that there is a mismatch of evidence in this instance as the economic model considers data from both pooled SIROCCO/CALIMA and ZONDA trials. Further after the first year, a significant proportion of patients in the benralizumab arm are defined as responders, who benefit from additional exacerbation rate reduction. We believe that this explains the difference in exacerbation rates and types in the model vs those in only SIROCCO/CALIMA and therefore that there is no under or overestimation.	**Action:** The comment has been removed.

Issue 7 Nocturnal awakenings, ERG report, pages 21, 31, 54-55, 57-59, 224-226

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
"While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted] Nocturnal awakenings are only one component of asthma control and asthma-related quality of life. Therefore, it is not appropriate to make generalisations about asthma control; and HRQOL based on one specific outcome, given that a beneficial effect was observed for benralizumab for overall ACQ-6; TAS scores, and AQLQ(S)+12. Further it	We agree that the observed reduction in nocturnal awakening	The ERG's statement could be misleading in the context of other	The ERG agree that the report wording highlighted here by the company

should be noted that in all three trials, the change in TAS was driven equally by improvement in daytime and nighttime asthma symptoms. A summary of symptom and asthma-related HRQOL questionnaire scores is shown in the table below:	s was small, but request that the statement regarding the negligible impact on asthma control and implications for HRQOL be removed	positive HRQOL outcomes	could be considered ambiguous. **Action:** The ERG have subsequently changed the wording in the report to "While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the ERG note a small and clinically negligible 6% reduction in nocturnal awakenings (reported in CSR only)" (p.21, p.31, p.137 of report)

Benralizumab Q8W versus placebo, ITT analysis	Total asthma symptom score, difference vs placebo	ACQ-6 score, difference vs placebo	AQLQ(S) +12, difference vs placebo
SIROCCO **N=1,205**	LS mean difference: -0.25 (95% CI: −0.45 to −0.06; p=0.012)	LS mean difference: -0.29 (95% CI: -0.48 to -0.10; p=0.003)	LS mean difference: 0.30 (95% CI: 0.10 to 0.50; p=0.004)
CALIMA **N=1,306**	LS mean difference: -0.23 (95% CI: −0.43 to −0.04; p=0.019)	LS mean difference: -0.25 (95% CI: -0.44 to -0.07; p=0.008)	LS mean difference: 0.24 (95% CI: 0.04 to 0.45; p=0.019)
ZONDA **N=220**	LS mean difference: -0.18 (95% CI: -0.51 to 0.16; nominal p=0.291)	LS mean difference: -0.55 (95% CI: -0.86 to -0.23; p=0.001)	LS mean difference: 0.45 (95% CI: 0.14 to 0.76; p=0.004)

Issue 8 Effect Modifier Selection used in MAIC (Matched Adjusted Indirect Comparison), pages 124 and 126

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
ERG report, section 4.4.4 (effect modifier selection), page 124 *"It was unclear whether the clinical input was only sought on the validity of a selection of variables that had already been made, rather than seeking open elicitation of potential effect modifiers from clinicians from the onset."* The selection of effect modifier was in line with the NICE Guide to the Methods of Technology Appraisal (Section 5.2.7) and NICE TSD 18 (Phillippo 2016) which explicitly state that effect modifiers must be 'pre-specified and clinically plausible,' and that effect modifier should either be identified from a review of the literature or from the clinical input. The effect modifiers were identified through various methods such as literature search, existing subgroup analysis from mepolizumab, benralizumab and reslizumab clinical studies and through clinical opinion. The clinical opinion was sought using an open elicitation method. Based on the clinical opinion additional effect modifiers such as 'nasal polyps' and 'BMI' were identified and considered for matching. Table 40 in ERG report (page 125) and in CS (please see below) indicates these two additional effect modifiers were considered for	These statements should be amended to provide clarity on the Effect Modifier Selection methods used.	To provide clarification that the selection of effect modifier was in line with the NICE Methods Guide and NISE TSD 18, specifically that: • Clinical opinion was sought using an open elicitation method • Effect	We do not consider this a matter of factual accuracy with regard to the content of the ERG report. The company submission was unclear about how clinical input was used in effect modifier selection, and therefore based on the information provided in the company submission, the ERG was correct to say that *"It was unclear whether the clinical input was only sought on the validity of a selection of variables that had already been made, rather than*

matching based on clinical opinion besides those already identified effect modifiers from literature. Please refer to the last column in the table below (yellow highlighted text). Additionally, the ERG highlighted the following on page 126 *"Moreover, the ERG noted from the above table that certain variables that were statistically significant – age, race, BMI, FEV1, nicotine status, and atopic status – were excluded as effect modifiers and not selected for matching in MAIC because there was not a significant imbalance between benralizumab and mepolizumab trials."* This statement is incorrect as BMI was identified by clinical opinion as an effect modifier and was considered for matching irrespective of the balance across the two populations. Concerning other variables such as age, race, FEV1, atopic status and nicotine status, these were not considered for matching as these were not considered as effect modifiers after clinical consultation.		modifiers that were balanced between benralizumab and mepolizumab trials were selected, where appropriate	*seeking open elicitation of potential effect modifiers from clinicians from the onset."* Furthermore, the ERG is satisfied that there are no factual inaccuracies in its assessment of effect modifier selection in the MAIC and that all disagreements are matters of opinion. The ERG has therefore not made amendments to these sections of its report. **No action required**

Table 40 Summary of selection of variables for matching in the MAIC

Variable	Definition	Statistical significance* (p<0.05)	Information available in MEPO trials	Difference between BENRA and MEPO trials	Effect modifier	Selected for matching
Age	Mean (SD)	No	Yes	No	-	No
Gender	Categories: male, female	Yes	Yes	Yes	-	Yes
Race	Categories: White, Asian, Black or African American	Yes	Yes	No	-	No
BMI	Mean (SD)	Yes	Yes	No	-	Yes (based on clinician opinion)

FEV1 predicted (%)	Mean (SD)	Yes	Yes	No	-	No
FEV1/FVC (%)	Mean (SD)	No	Yes	No	-	No
FEV1 reversibility (%)	Mean (SD)	No	Yes	No	-	No
ACQ score	Mean (SD)	Yes	Yes	Yes	-	No (different ACQ scale versions used)
No. of exacerbations in previous 12 months	Categories :2 exacerbations, >2 exacerbations	Yes	Yes	Yes	Yes	Yes
Nicotine status	Categories: former, never	Yes	Yes	No	-	No
OCS use at baseline	Categories: yes, no	Yes	Yes	Yes	Yes	Yes
EOS count	Categories: EOS<300/µL, EOS≥300/µL	Yes	Yes	Yes	Yes	Yes
IgE status	Categories: IgE ≤30 IU/mL, IgE >30-≤700 IU/mL, IgE >700 IU/mL	Yes	Yes	Yes	Yes	Yes
Atopic status	Categories: yes, no	No	No	-	-	No
Nasal polyps	Categories: yes, no	Yes	Yes	No	-	Yes (based on clinician opinion)

Benralizumab for treating severe asthma

Errata

Location in report	Original text	Corrected text
Section 1.3, p. 20	The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both pooled trials only for the Asian population. While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the ERG noted a small clinically negligible 6% reduction in nocturnal awakenings (reported in SIROCCO CSR only).	The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both SIROCCO and CALIMA trials only for the Asian population.
Section 1.5.2, p. 24	Mortality due to asthma is also a key parameter in this appraisal.	It is also an important parameter in this appraisal.
Section 1.5.2, p. 25	In the ERG's analysis, all probabilities related to asthma-induced death were reduced except those in patients of 45-100 years old (for OCS burst and ER visit) and 65-100 years old (for hospitalisation) as it was not possible to conduct extensive searches for relevant sources due to time constraints (Table 60)	In the NRAD report which was used by AstraZeneca to parameterise asthma mortality risk in hospital settings, it is stated that the majority of people (57%) who died from asthma between February 2012 and January 2013, "*were not recorded as being under specialist supervision during 12 months prior to death*". However, the patient population considered in this appraisal are patients with severe asthma *who have been on asthma treatment during the previous 12 months*. In this analysis, only the probabilities of asthma-related death in hospitalised patients from 45-54 and 55-64 age categories were reduced by factor of 2.5 (see Table 60). The probabilities of asthma death in patients 45 years of age and older requiring OCS burst or ER visit, and hospitalised patients ≥65 years of age were kept unchanged as it was not possible to conduct extensive searches for relevant evidence sources due to time constraints.

Location in report	Original text	Corrected text
Section 1.5.3, p. 26		However, under a PAS price for mepolisumab, this assumption had a moderate effect on the cost-effectiveness of BEN vs. MEPO.
Section 1.5.4, p. 26		The ERG noted (p. 164, company's submission): "In order to calculate the percentage of patients in each population who would be dependent on mOCS at baseline in UK clinical practice, an analysis of the Kerkhof 2017 paper, a UK observational research study, was undertaken. For a full description of the baseline characteristics refer to Table 22". However, the proportions reported by Kerkhof - 16.5% in patients 18-64 y.o. and 17.1% in patients >=65 y.o. - were substantially lower than those in the company's base case. Also, as shown in Table 22 (company's submission) which the company referred to, *only about 23% of patients in pooled SIROCCO/CALIMA* dataset were on mOCS at baseline.
Section 1.5.7, p. 28		Of note, in the MEPO appraisal, the annual attrition rate was 10%.
Section 1.5.8.1, p. 29		In the appraisal of mepolizumab, committee considered that utilities should be age-adjusted, and this adjustment was incorporated in the updated base case (p. 73, committee papers dated 1 December, 2016).
Section 1.5.8.2, p. 29		In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) [16]. In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely *less than the model cycle of 4 weeks*.
Section 1.3, p. 31	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted]. This may have implications for HRQoL.	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted]
Section 1.6.2.2, p. 32	The company assumed that the same percentage of patients	

Location in report	Original text	Corrected text
	taking mOCS respond to benralizumab and reslizumab. The ERG noted, however, that these drugs have different mechanisms of action, and therefore, this assumption would need further clarification (Section 5.2.2.1).	
Section 4.1.5, p. 58	[redacted]	
	In summary, reporting bias is a concern in the ZONDA trial due to incomplete reporting of data in the trial publication and appendices, particularly with regard to nocturnal awakening and rescue medication [redacted]	
Section 4.2.1, p. 75	However, the difference in total asthma score reduction (-0.25), though statistically significantly, did not reach MCID.	However, the difference in total asthma score reduction (-0.25), though statistically significantly, did not reach Minimum Clinically Important Difference (MCID) defined as score changes of 0.5 point or more for ACQ-6 and AQLQ(S)+12 [13].
Section 4.2.1, p. 78	Data in this main analysis included patients with two exacerbations in the year preceding trial enrolment.	Data in this main analysis included also patients with two baseline exacerbations in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations).
Section 4.2.1, p. 80	The ERG believed that a meta-analysis of the summary estimates derived from the analysis of each trial's individual patient data would provide a more precise estimate without losing trial identity.	The ERG believed that a fixed-effects meta-analysis of the summary estimates derived from the analysis of each trial's individual patient data would give the same result as the pooled analysis but a random effects meta-analysis would provide a wider confidence interval. However, the ERG noted that the relationships were not statistically significant as there were overlaps in all 95% CI.
Section 4.2.1.1,		The reduction in AER in the subgroup population is similar to result from the ITT

Location in report	Original text	Corrected text
p. 86		analysis of benralizumab Q8W from the SIROCCO (51%) trial but higher than AER reduction reported for the ITT analysis of benralizumab Q8W from the CALIMA trial (28%).
Section 4.2.1.1, p. 87	[redacted]	[redacted]
Section 4.6, p. 137	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the [redacted]	The reduction in AER for the pooled subgroup analysis was similar to that from the ITT analysis of the SIROCCO trial (51%) but higher than the AER reduction from the ITT analysis of the CALIMA trial (28%). No death was considered related to investigational product.
Section 5.2.2.1, p. 146		The company stated in the factual accuracy check pro forma: "*The final guidance for mepolizumab states that patients should "continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control." This is the continuation criteria used within the company model and the [redacted] of patients who respond to mepolizumab is reflective of this.*" The CS reads: "*As the data regarding the percentage of patients responding to*

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		mepolizumab is not specific as to whether it applies to the non mOCS or the mOCS population and it is referenced to the MENSA/DREAM trials it is assumed that this percentage relates to the non mOCS population and an assumption is made that the percentage of responders in the mOCS population is equal that of benralizumab."
Section 5.2.2.1.1, p. 147		In the MEPO appraisal, the annual attrition rate was assumed to be 10% (p. 81, committee papers dated 1 December, 2016).
Section 5.2.6.1.2, p. 159	According to the results of the pooled SIROCCO/CALIMA subgroup analysis shown in Table 20, the marginal annual exacerbation rates for BEN and placebo were 0.85 and 1.83, respectively; the annual rates of ER visits were 0.05 and 0.15 for BEN and placebo, respectively; hospitalisation rates were *not reported*, but the relevant RR was 1.01; and exacerbation rates requiring OCS burst were also missing in the CS. For the BEN vs. SOC comparison, the company's model predicted a twice higher rate of hospitalisation in SOC patients; underestimated the rate of exacerbations requiring ER visit, and overestimated OCS rate in BEN patients.	
Section 5.2.6.3, p. 161		For the comparison vs. SOC, the company assumed that 30.1% and 10.7% of patients in the BEN and SOC arms, respectively, discontinue mOCS at 28 weeks after treatment initiation. In the MEPO comparison, the respective proportions for BEN and MEPO were 20.2% and 9.82%; these proportions were not reported in the company's submission (they were taken from the company's model). In MEPO appraisal, to account for benefits of mOCS sparing, the company applied a reduction of £4,000-£9,000 to the ICER in a scenario analysis, referring to the appraisal of

Location in report	Original text	Corrected text
		omalizumab (p. 133, committee papers dated 1 December, 2016). In the RESLI appraisal, the model did not incorporate stopping or reducing the dose of oral corticosteroids, because the dose was kept constant in the pivotal trials (p. 13, committee papers dated 3 February, 2017) [8].
Section 5.2.6.5.2, p. 165		Importantly, *only adjustments made to 45-54 and 55-64 age categories for hospital admissions were effectively used in the ERG's base case* since the modelled age at treatment initiation was 50 years. In the updated base case for the MEPO appraisal, mortality rates in hospitalised patients from these age categories were 0.0092 and 0.0152, respectively; the probability of death in patients 65+ was 0.0455 (p. 75, committee papers dated 1 December, 2016). In RESLI appraisal, the asthma mortality was modelled based on Roberts et al. (2013) [2] (p. 32, committee papers dated 20 July, 2017). The authors reported odds ratio estimates from a logistic regression model for asthma-related mortality *within 30 days from hospital admission for asthma.* The following odds ratio estimates were used: - 2.4 for 45-54 age group - 6.3 for 55-64 age category - 12.3 for 65+ patients The 18-24 age group was the reference category.
Section 5.2.7.1, p. 168		Of note, in the RESLI appraisal, utilities reported by Willson et al. (2014) [49] and Lloyd et al. (2007) [16] were used.
Section 5.2.7.2, p. 170		In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) (p. 10, committee papers dated 1 December, 2016). In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely less than the model cycle of *4 weeks* (p. 57, committee papers dated 20 July, 2017).