Benralizumab for treating severe asthma

A Single Technology Appraisal

Produced by

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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

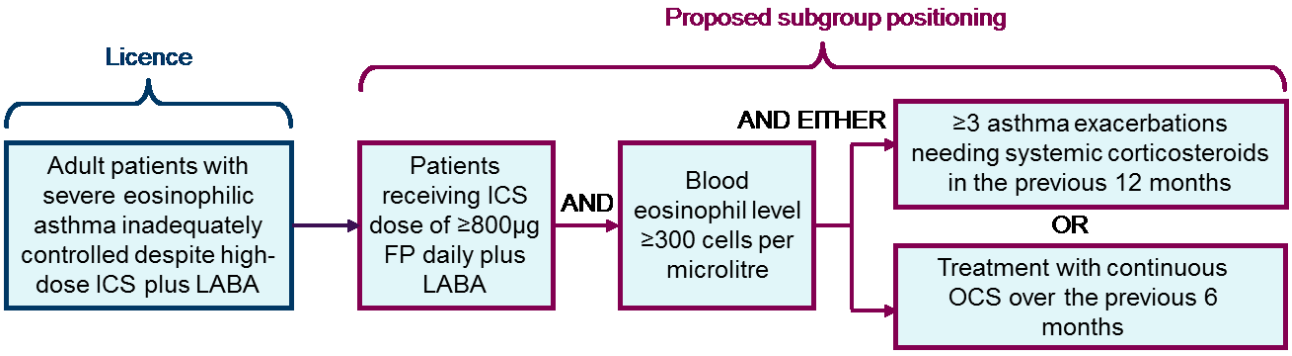
- 3 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months

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	MEPO + SOC	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	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

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

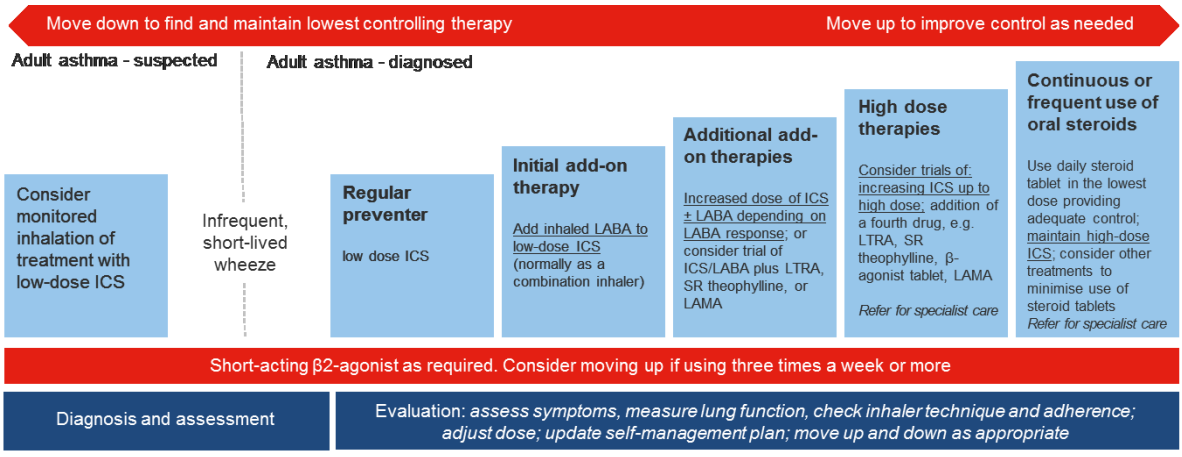
In the UK, the most commonly used treatment guidelines are those from BTS/SIGN and those recently published by NICE. The aim of asthma management is control of the disease. In BTS/SIGN guidelines, complete control of asthma is defined as [23]:

- 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]

[redacted]. Data from the CSR also

[redacted]

Data reported in the CSR

[redacted]

Therefore these data from the SIROCCO trial suggested

[redacted] The ERG's clinical expert, David Halpin, advised that most clinicians would not consider

[redacted] 113 [redacted] 113 [redacted].

These data from the SIROCCO trial suggested

[redacted]

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

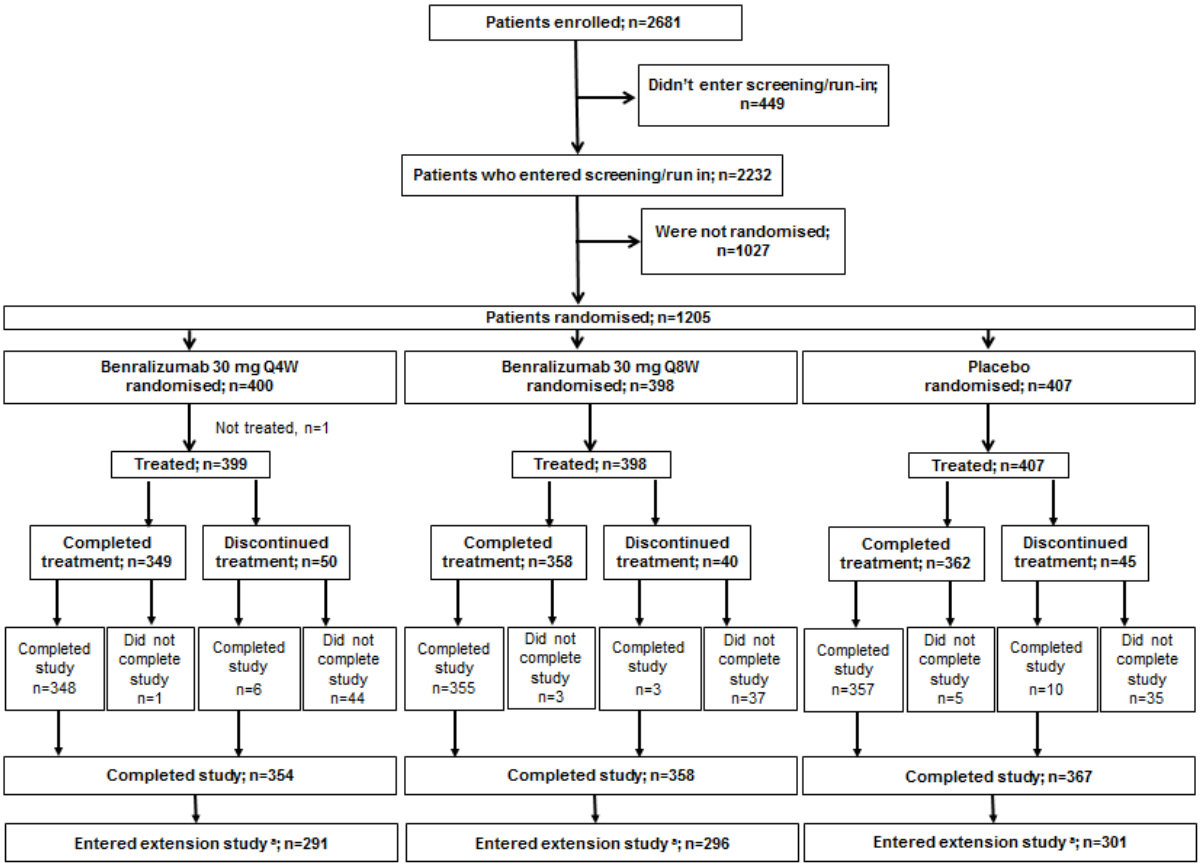
In SIROCCO and CALIMA, pre-specified subgroup analyses assessed the exacerbation rate in subgroups of clinical relevance. A post-hoc analysis was also conducted in the primary analysis population for the purposes of the CS, to assess the treatment effect of a history of at least three exacerbations experienced 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

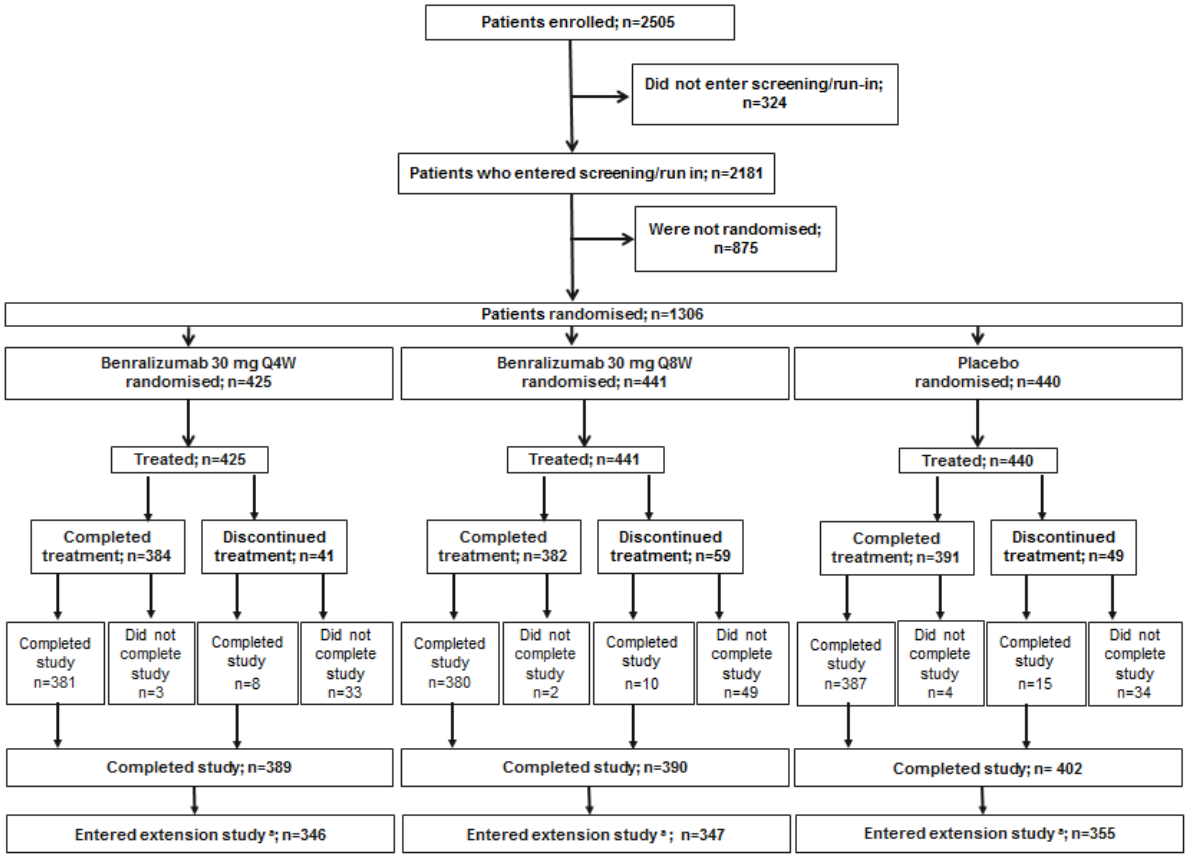
Figure 3 Participant flow in the SIROCCO trial



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.

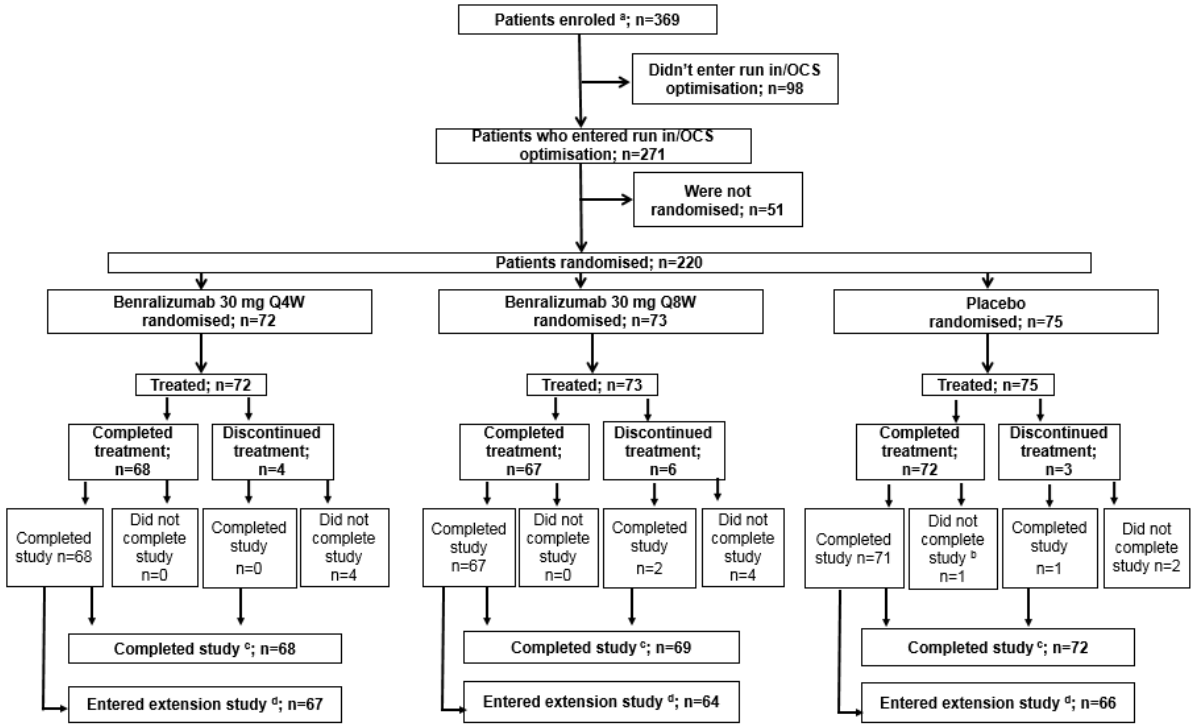
Figure 4 Participant flow in the CALIMA trial



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).

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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.

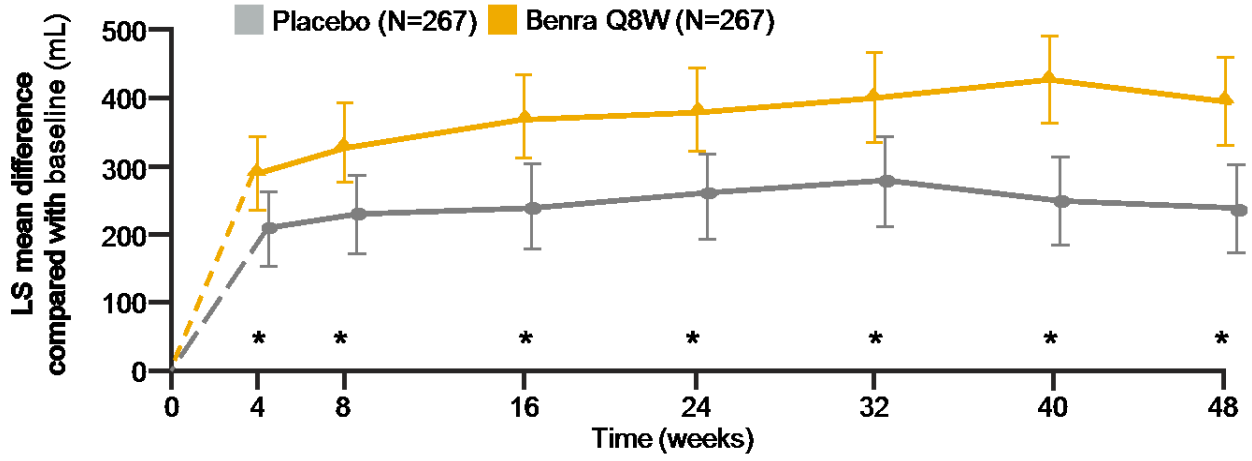
§ Numbers of patients at 48 weeks.

¶ 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).

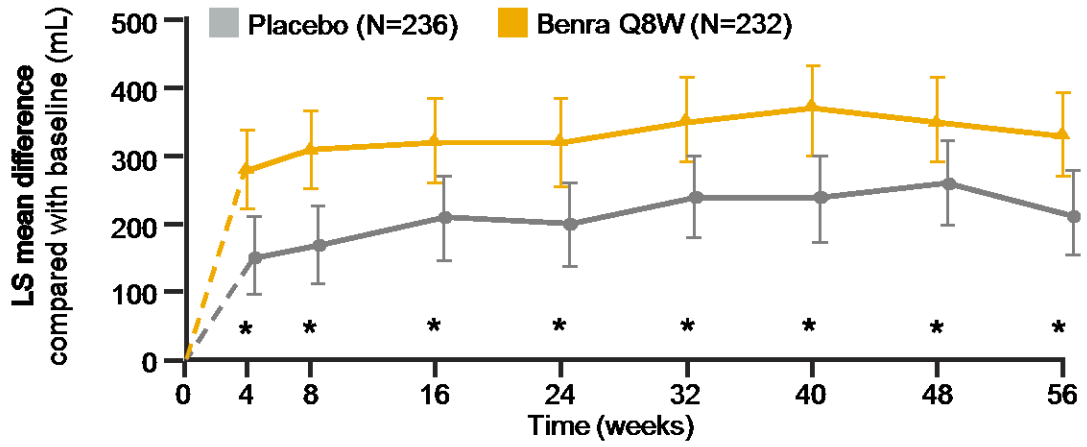
* Estimates calculated using a negative binomial model with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.

† 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

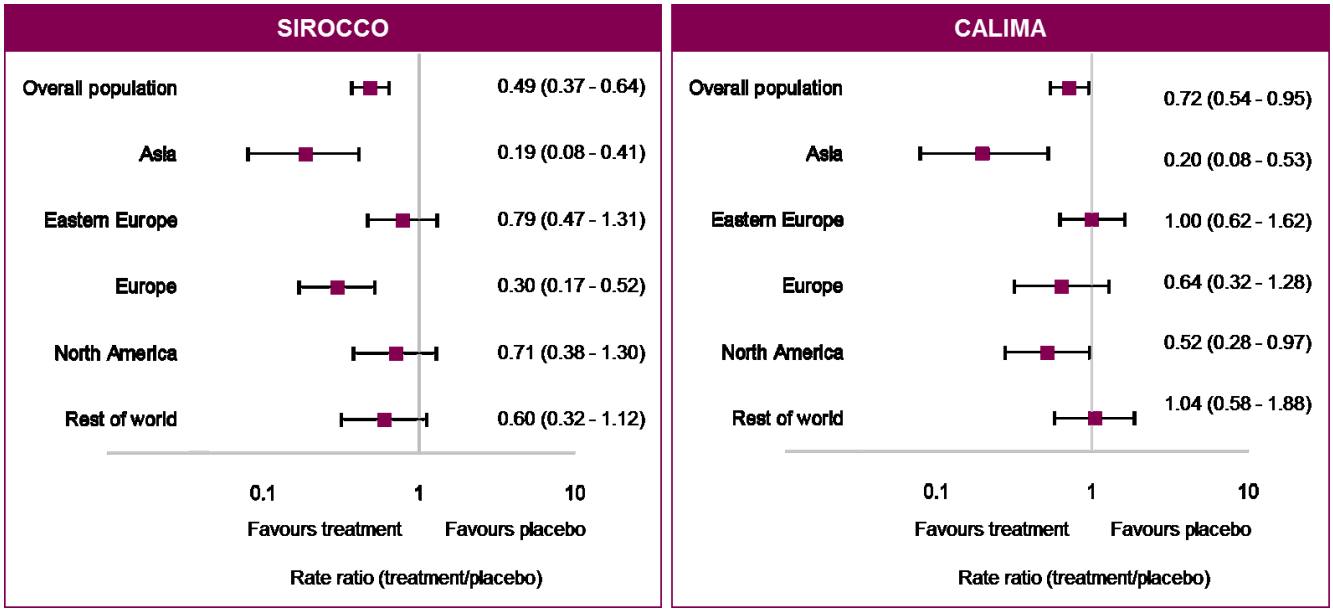
who had very low rates of exacerbations during the preceding year before study compared to the SIROCCO trial. However, the submission showed that the proportion of patients who had ≥ 3 exacerbations in the previous year before the study were similar in CALIMA (39.4%) and SIROCCO (41.4%) Q8W. Also, stratified 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

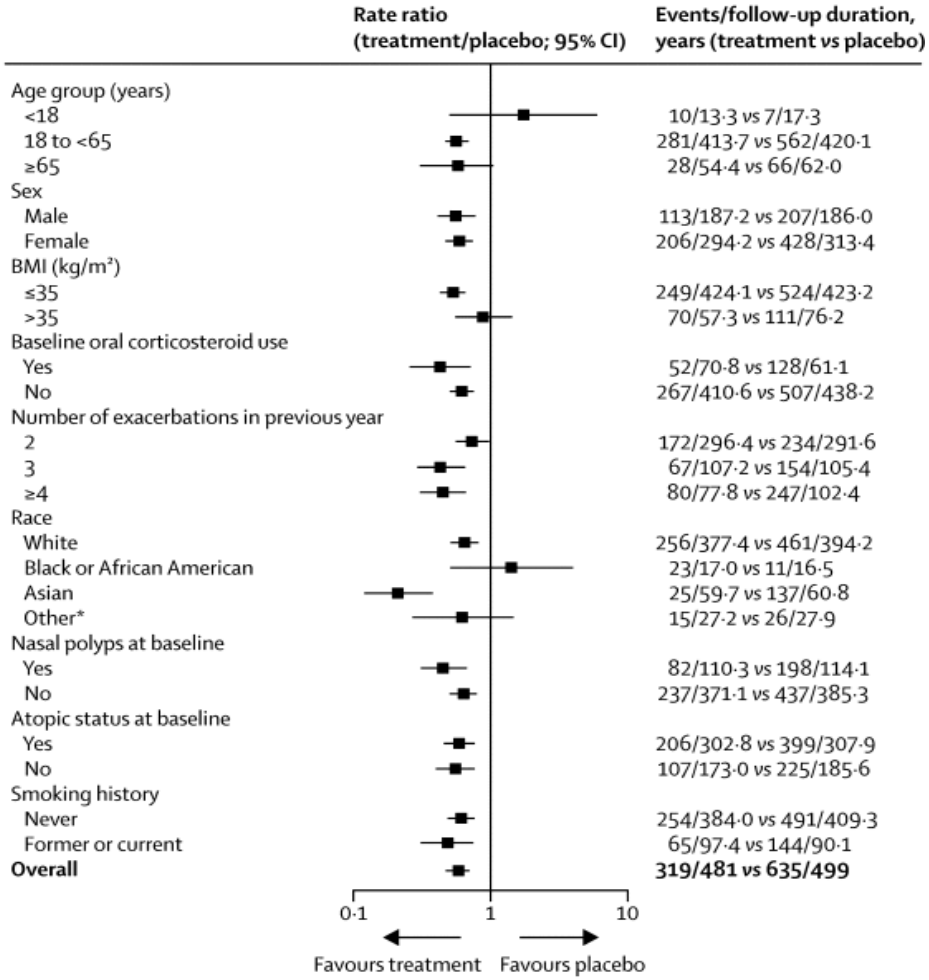
Pooled SIROCCO and CALIMA

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)

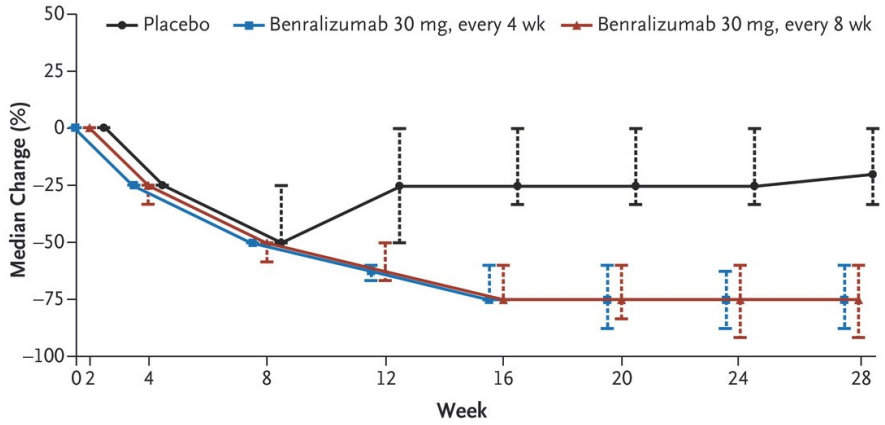
	Placebo (n=777)	Benralizumab Q8W (n=762)
≥0 cells per µL		
Number of patients analysed	770	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·55 to 0·75)
p value *vs* 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] 21 [redacted]

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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]

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	BENRA Q8W 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

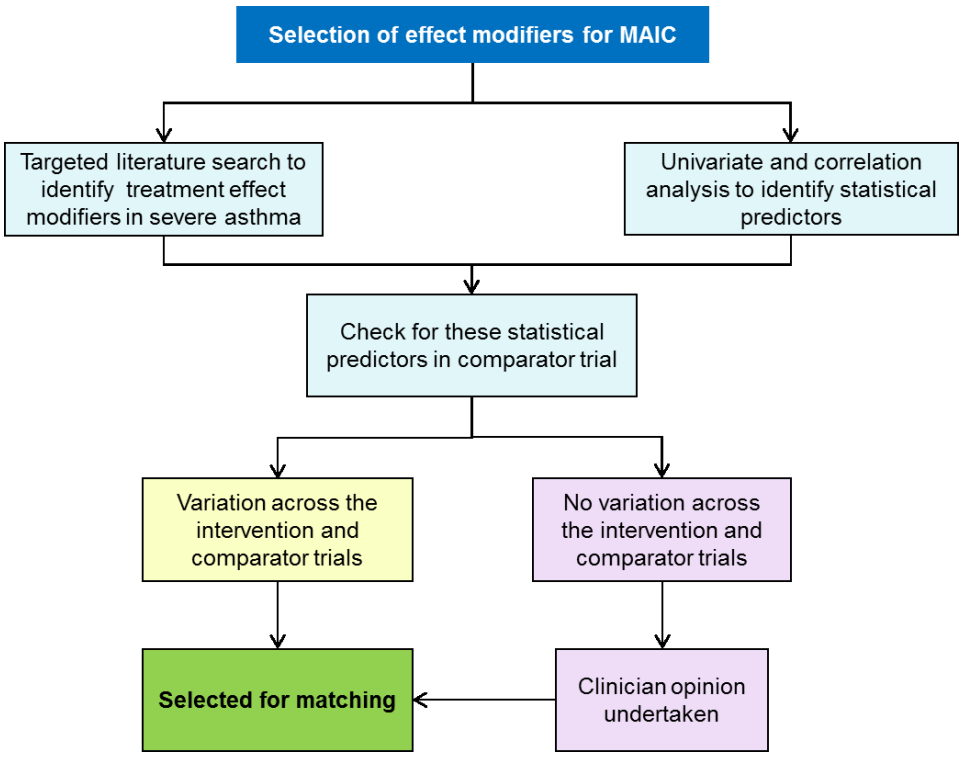
An important step in a MAIC analysis, according to NICE DSU recommendations, is the selection of effect modifiers and prognostic factors. This material was covered in detail in the Appendix of the CS (Section D.1.2, pp.361-365, pp.383-387). The NICE DSU recommendations stated that all known effect modifiers 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] 48

[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

[redacted] 19

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

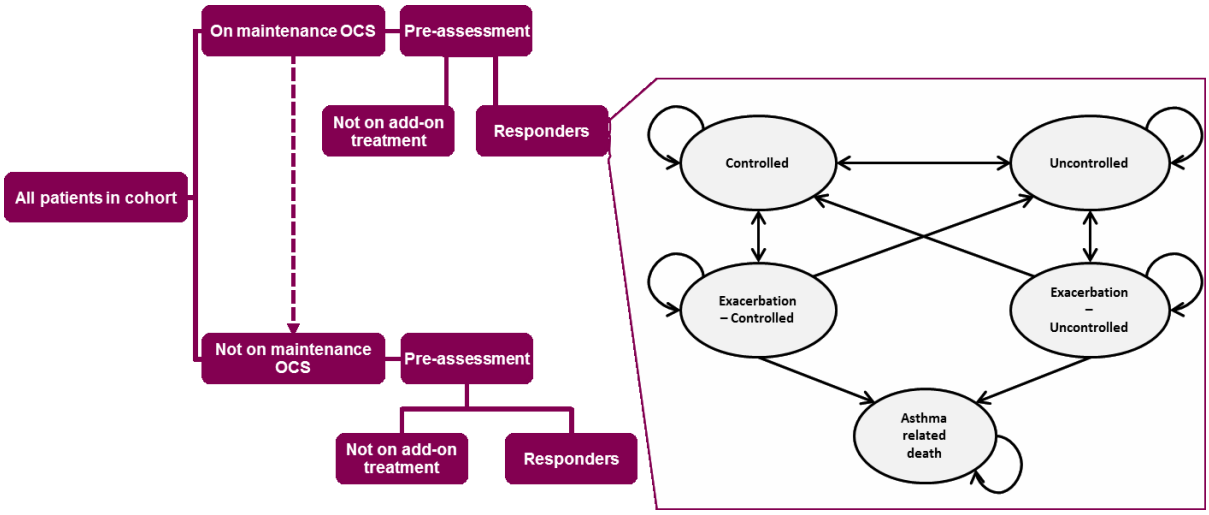
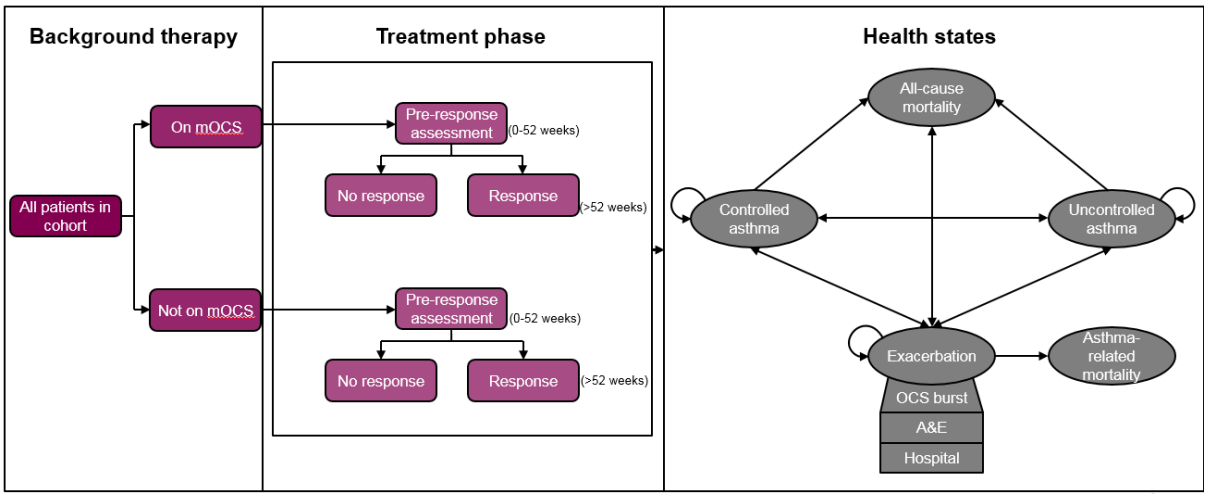


Figure 21 **Model structure as reported in company submission report**



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

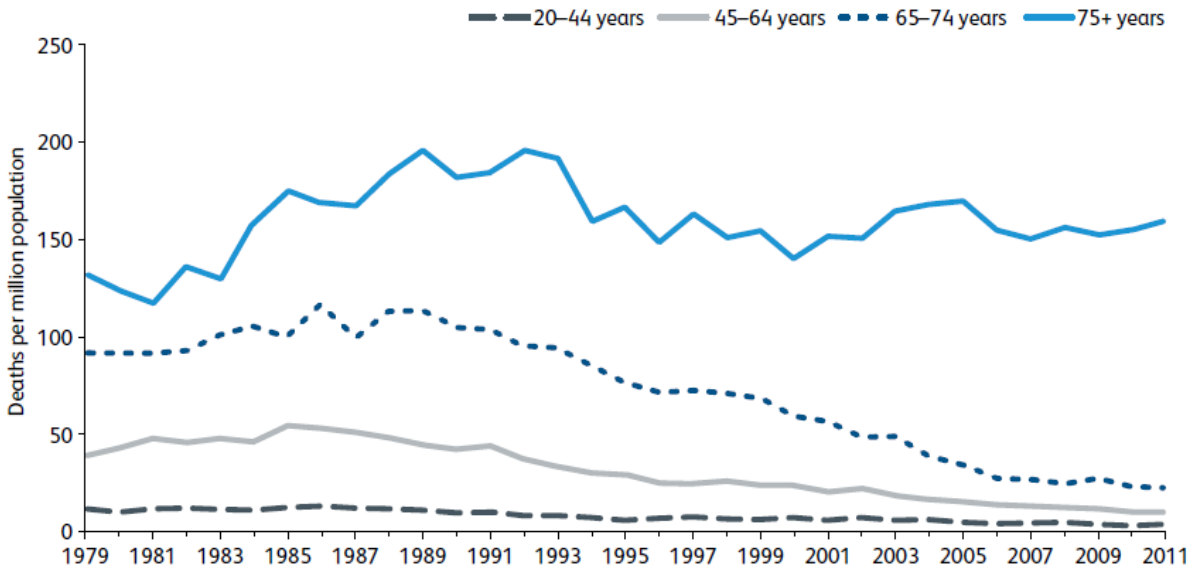
The impact of these assumptions was explored by AZ in a scenario analysis where asthma related mortality was set to zero. The ICER for comparison vs. SOC increased from £34,284 (base case) to £67,260 per QALY.

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.

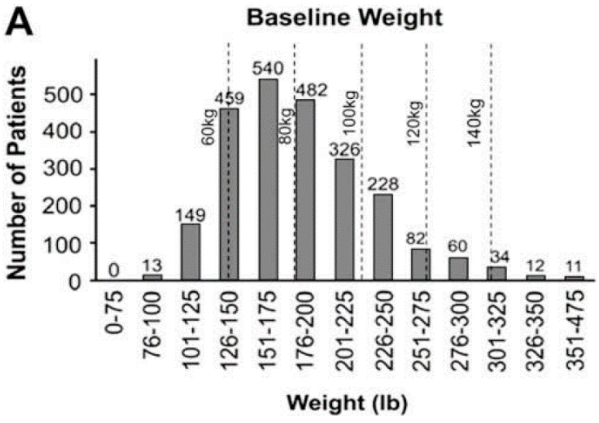
Reslizumab

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

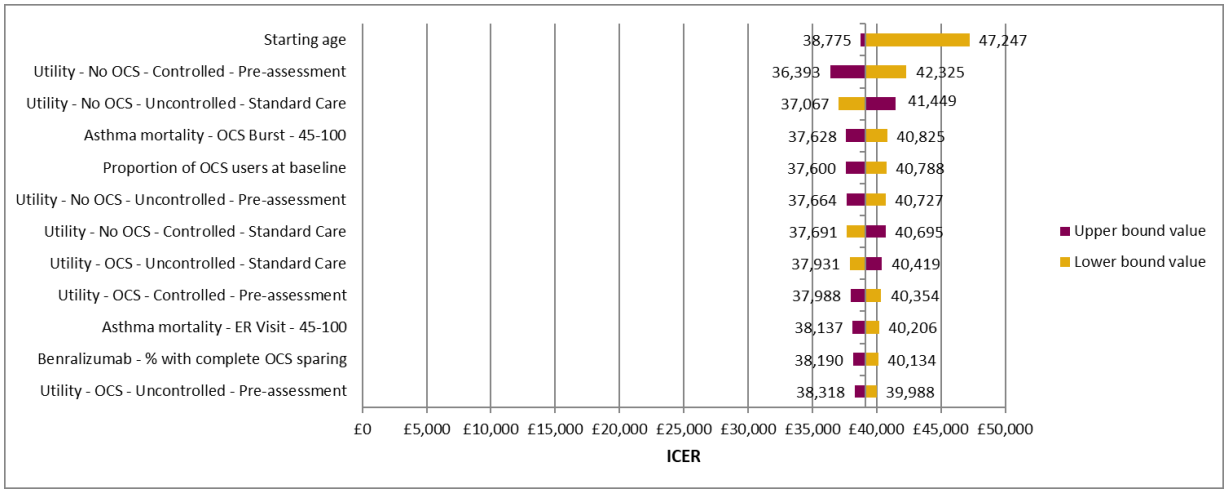
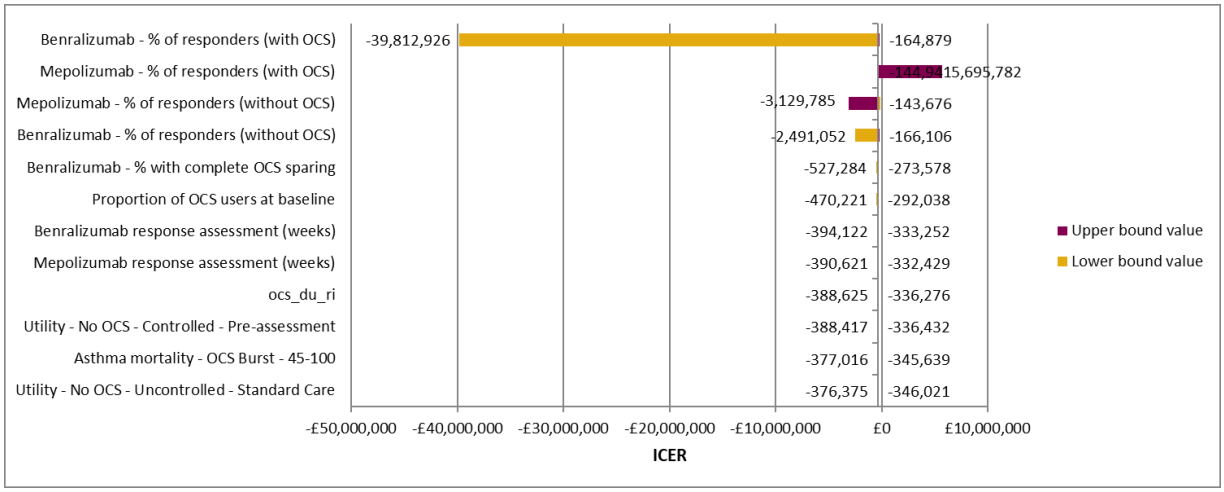


Figure 26 Tornado diagram for the ERG's base case vs. mepolizumab



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

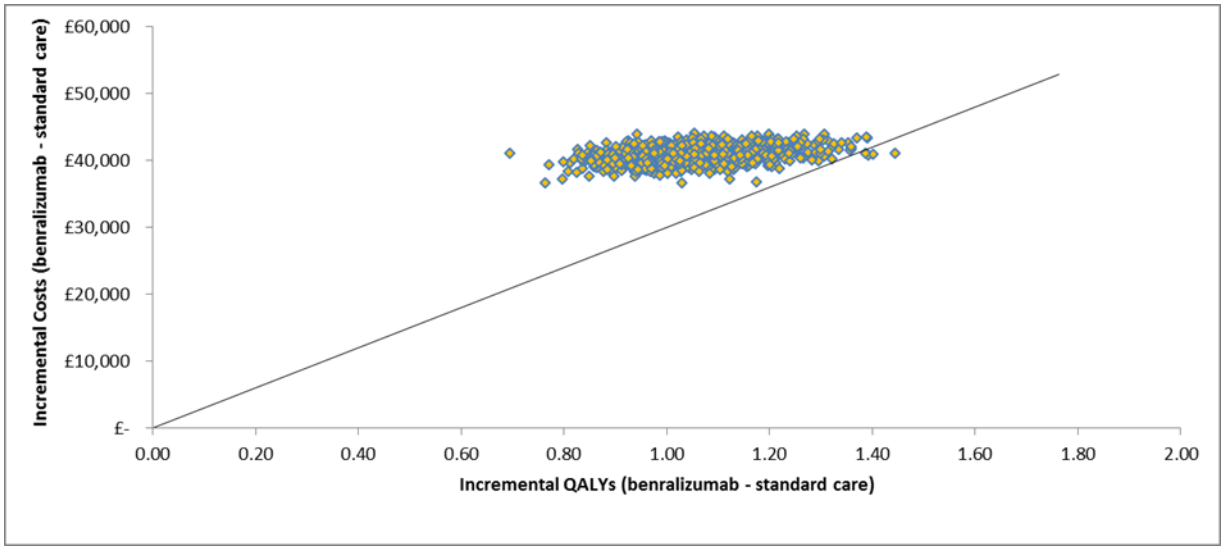
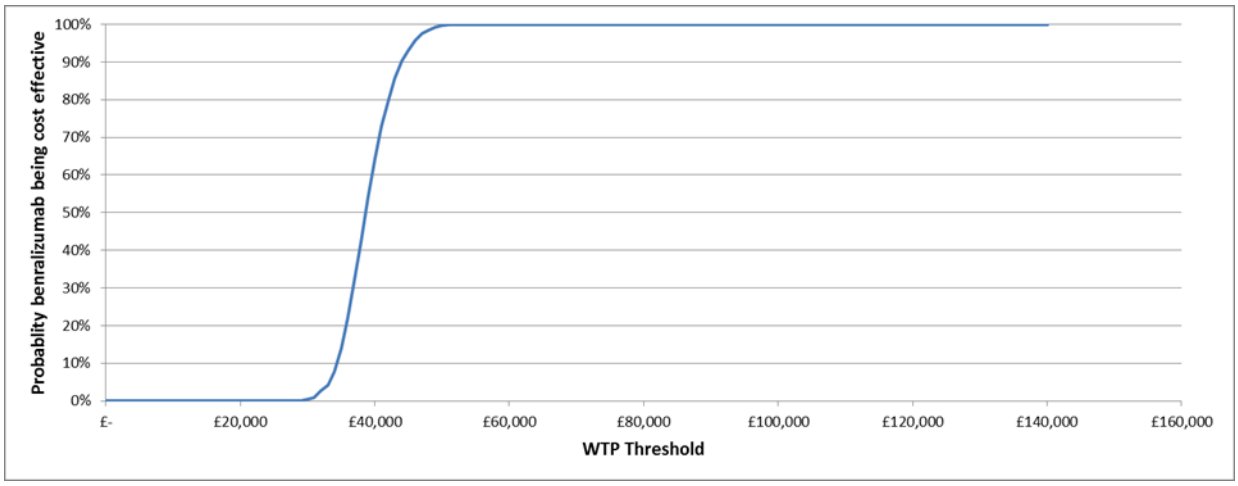


Table 78 ERG's base-case PSA vs. SOC

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

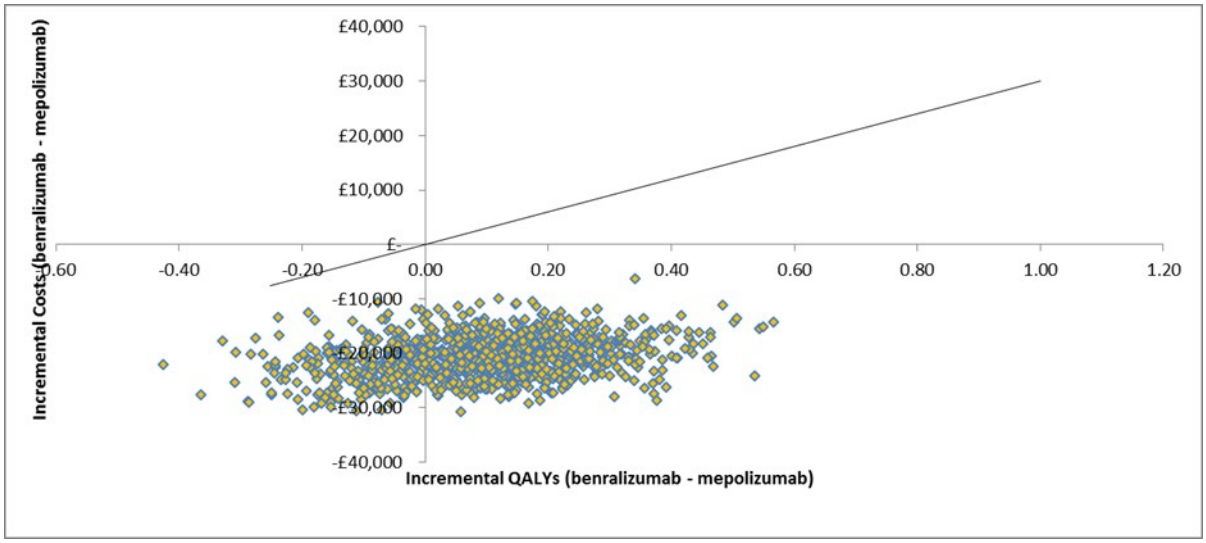
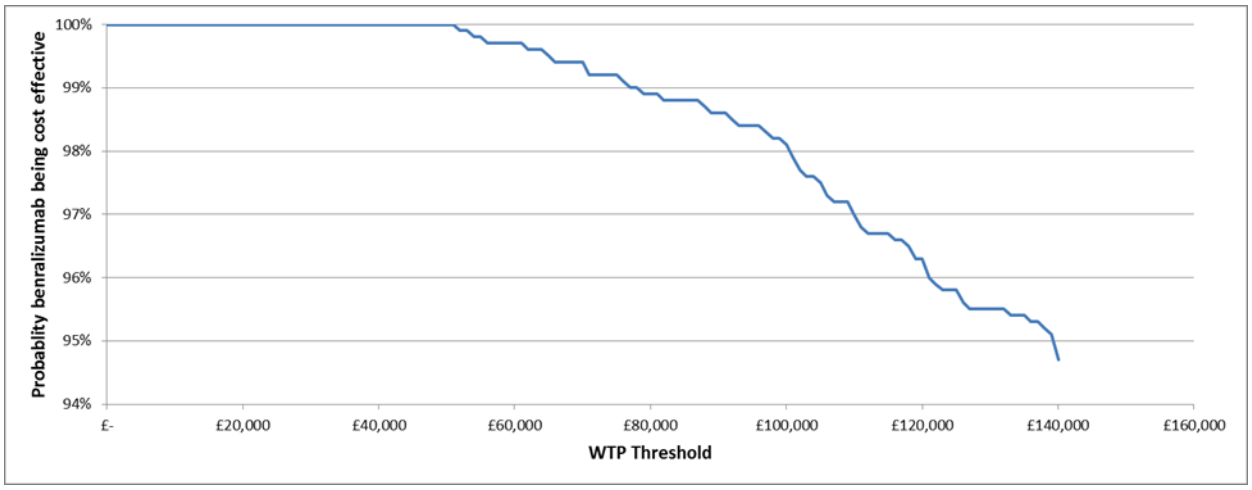


Table 79 ERG's base-case PSA vs. mepolizumab

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

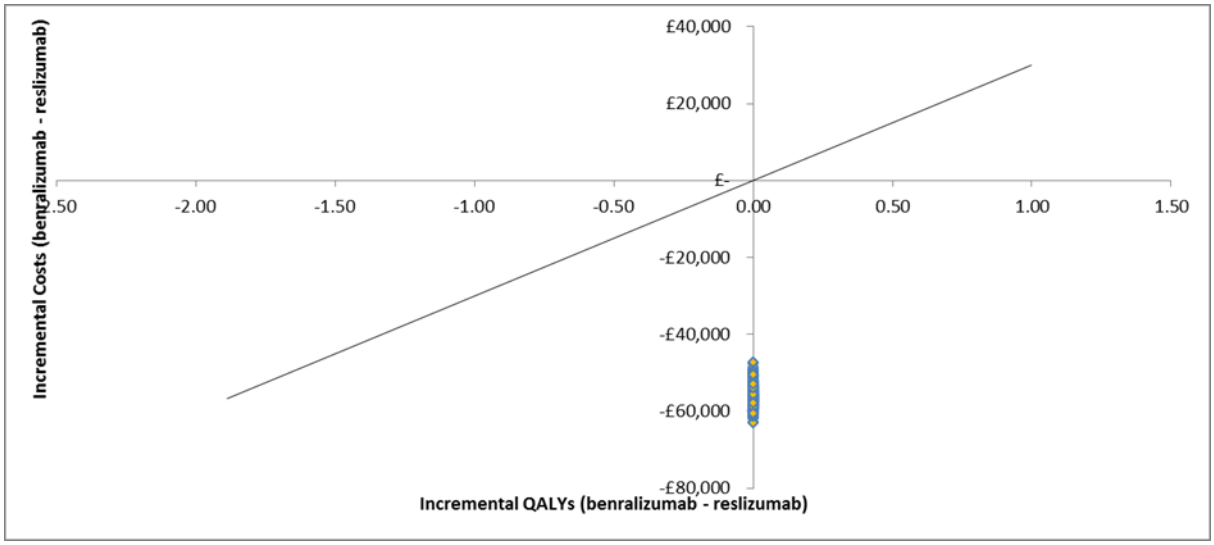
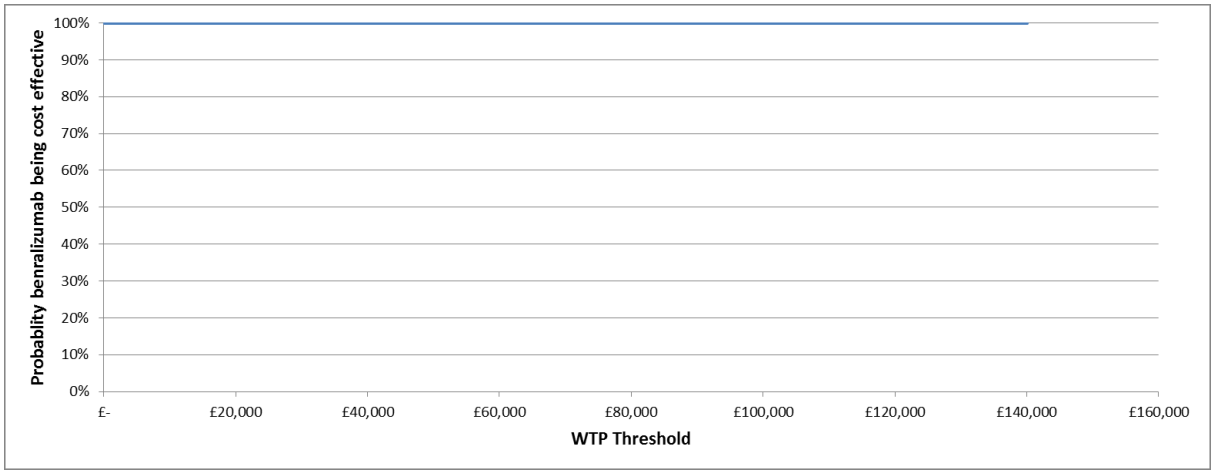


Table 80 ERG's base-case PSA vs. reslizumab (using reslizumab list price)

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.

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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

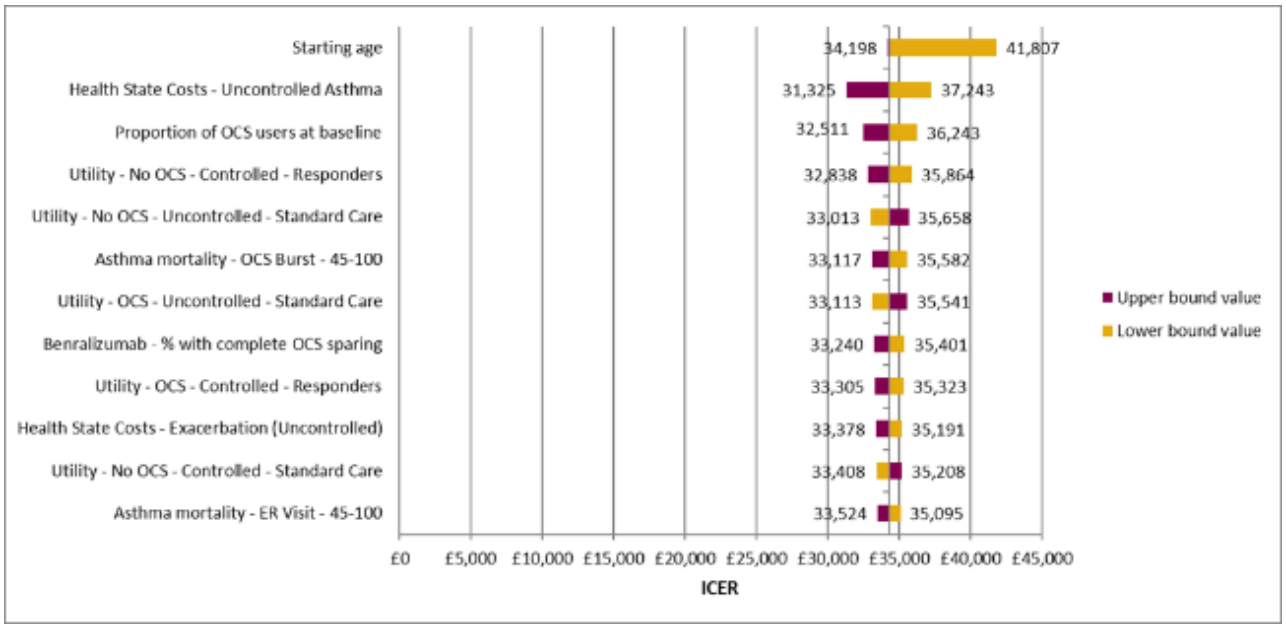

Figure 33 DSA vs. SOC from company

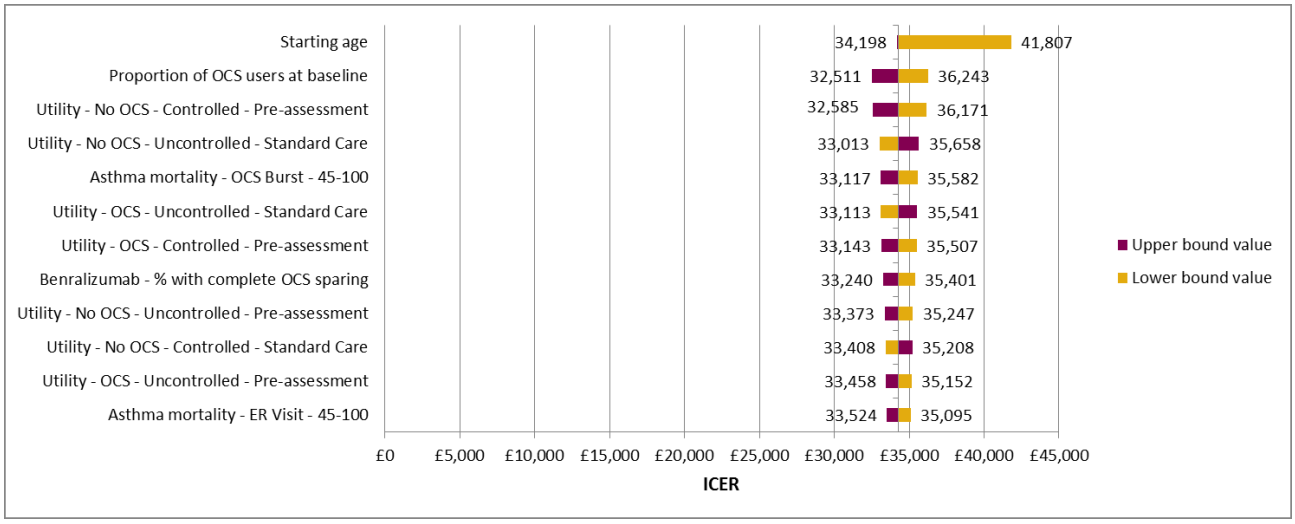

Figure 34 DSA vs. SOC run by the ERG (with corrected 20% limits)

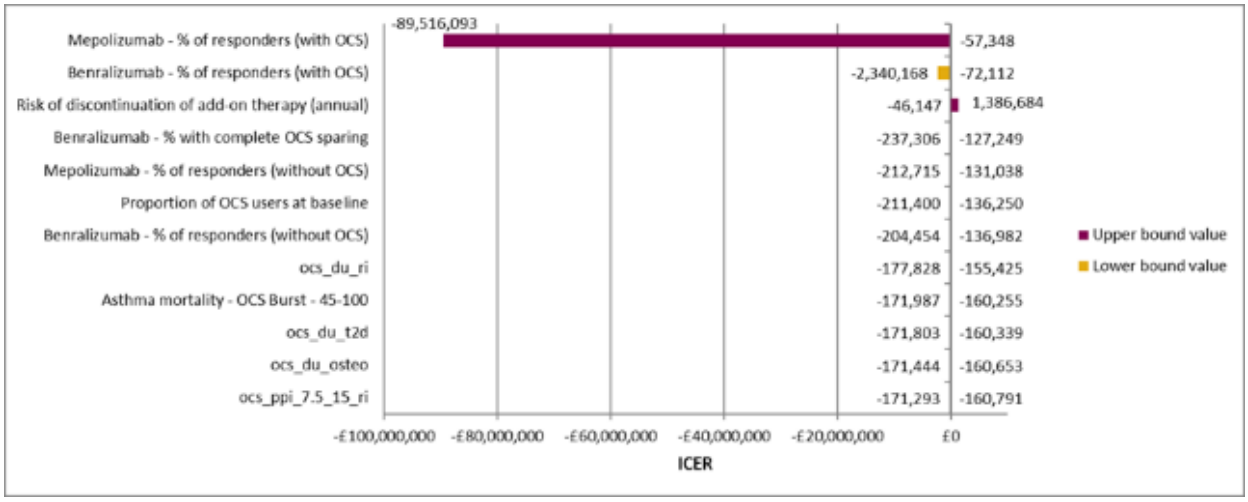

Figure 35 DSA vs. mepolizumab from company

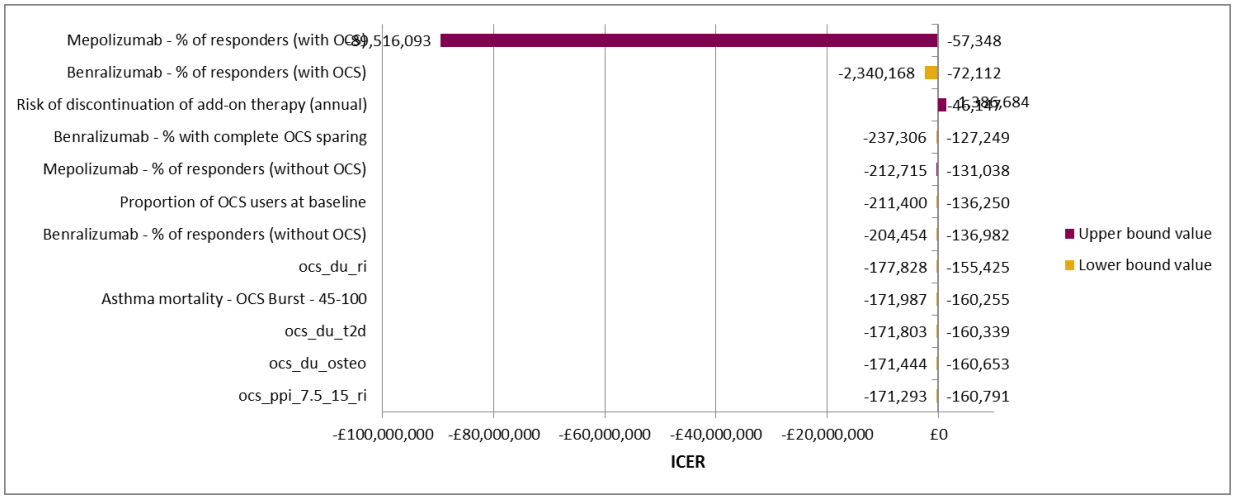

Figure 36 DSA vs. mepolizumab run by the ERG (with corrected 20% limits)

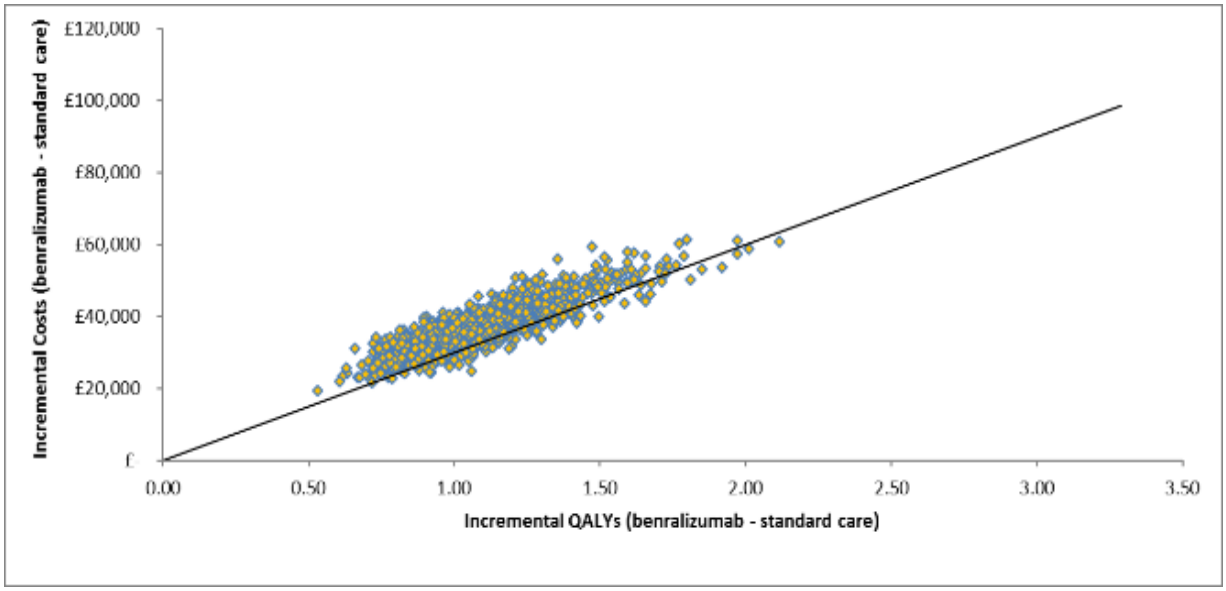

Figure 37 PSA vs. SOC from company

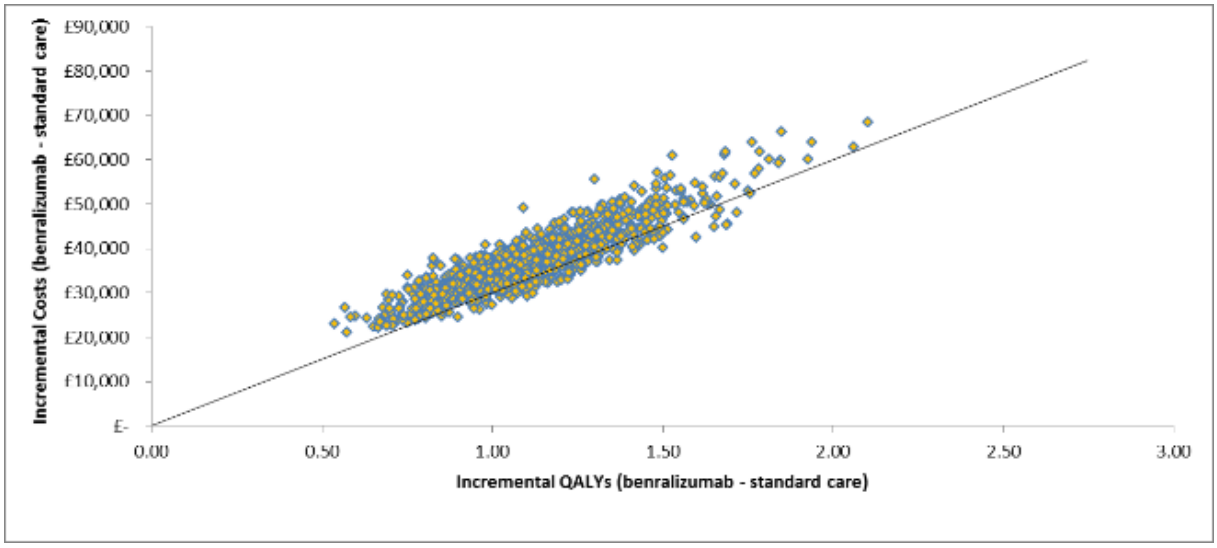

Figure 38 PSA vs. SOC run by the ERG

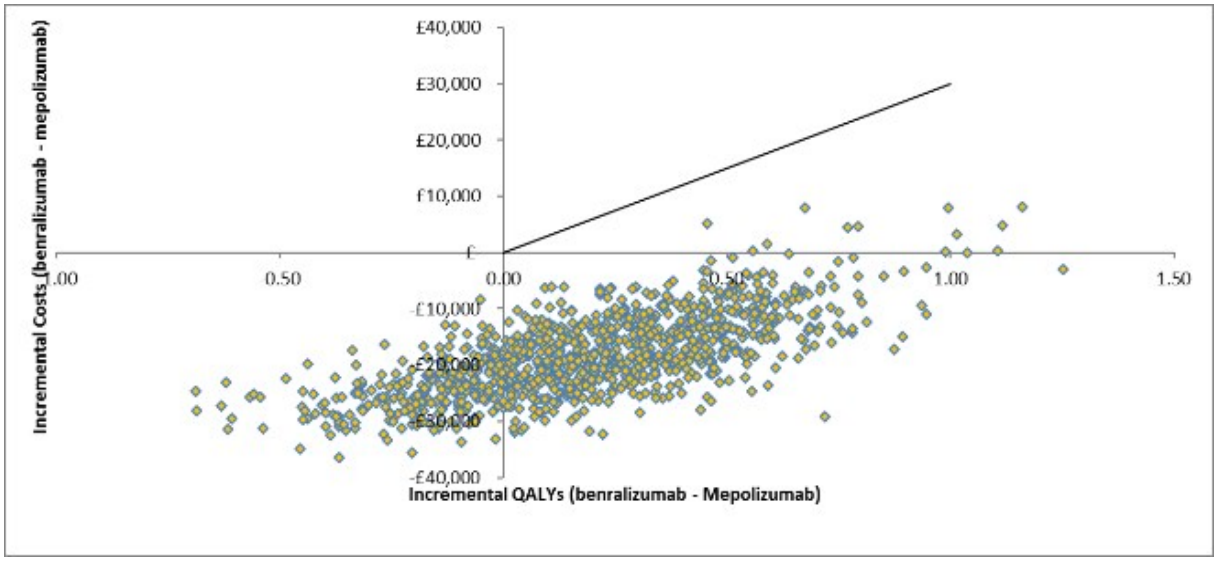

Figure 39 PSA vs. mepolizumab from company

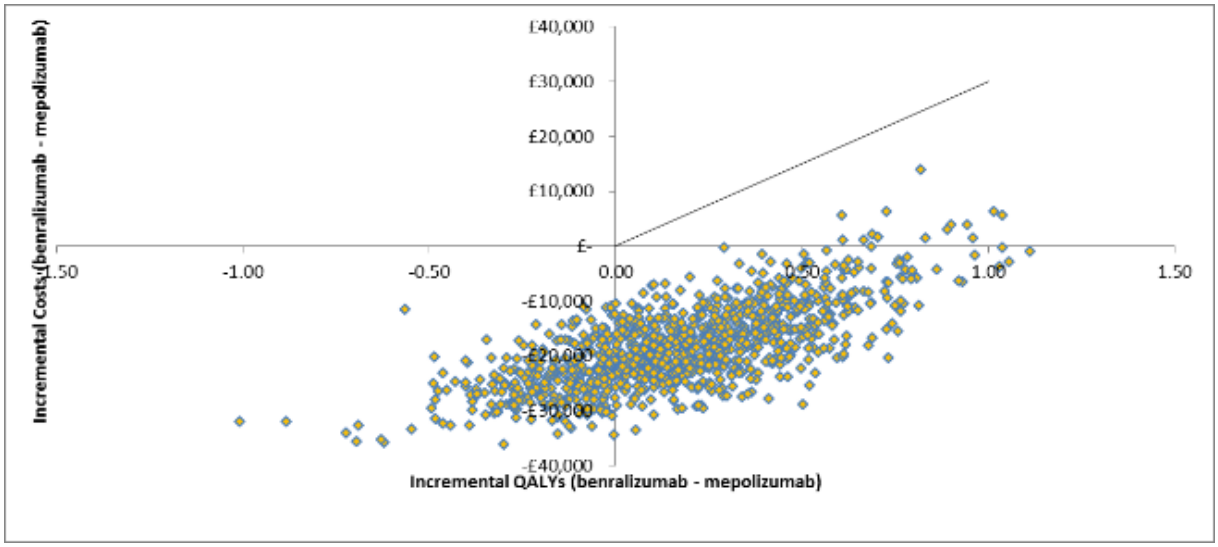

Figure 40 PSA vs. mepolizumab run by the ERG

Appendix 6. Additional clinical effectiveness data

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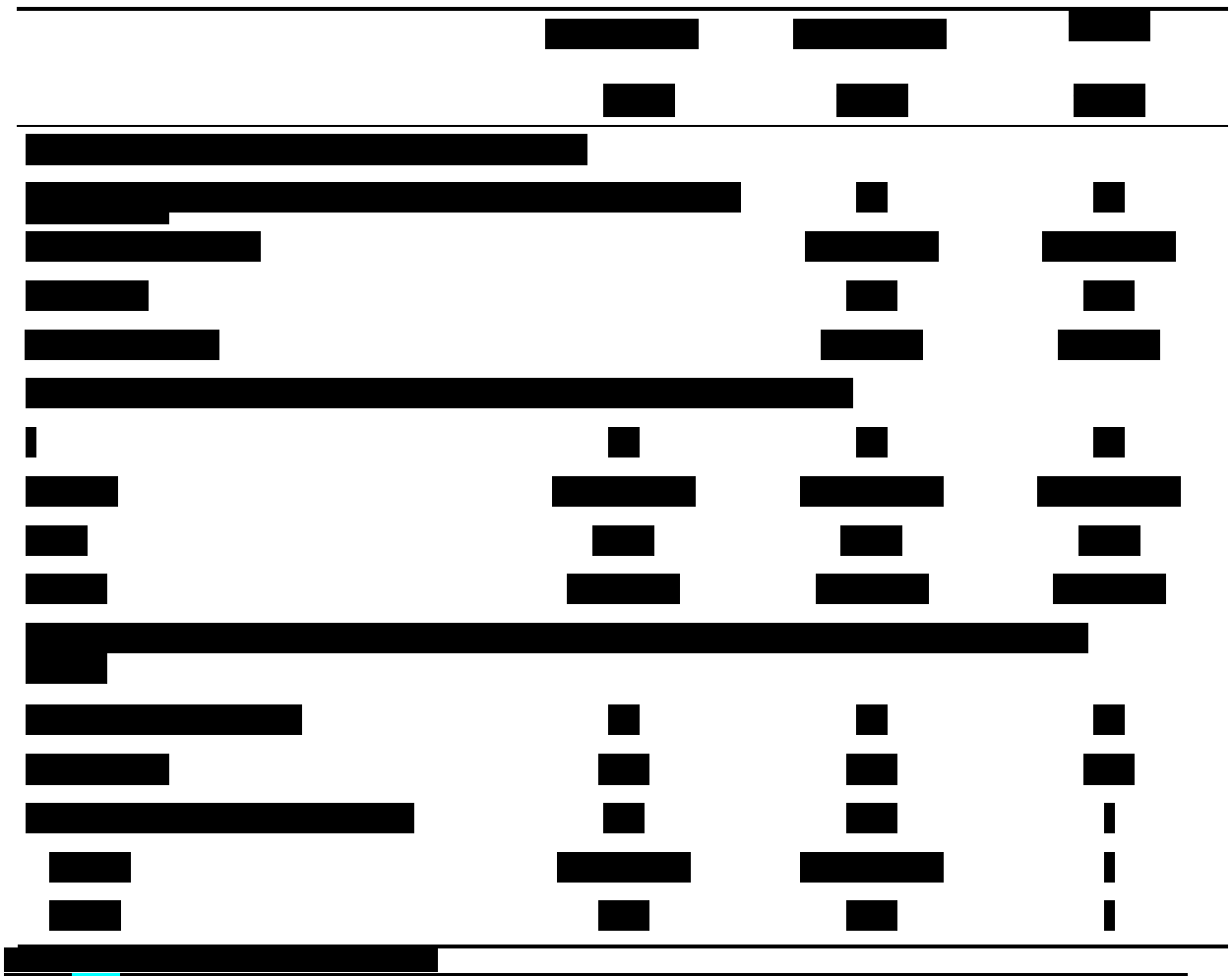

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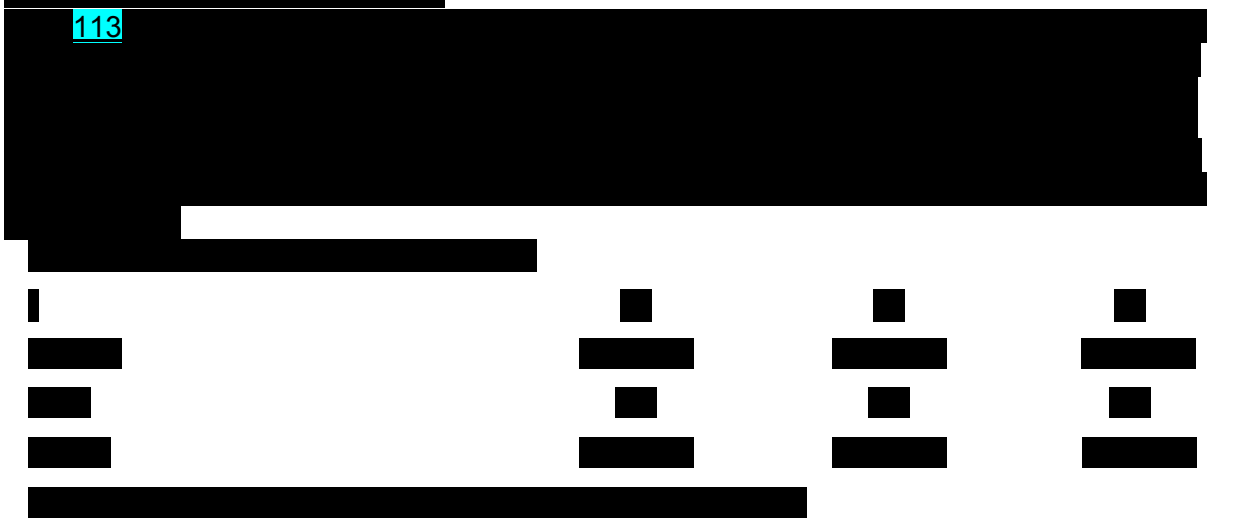

[redacted]

[redacted]

115 [redacted]